

78-WEEK TOXICITY AND CARCINOGENICITY  
STUDY IN MICE

1,2-DIBROMO-3-CHLOROPROPANE

FINAL REPORT

Submitted to

Dow Chemical Company  
Midland, Michigan



**HAZLETON**

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Hazleton 1978 B

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**HAZLETON**  
LABORATORIES AMERICA, INC.

SPONSOR: Dow Chemical Company

DATE: November 3, 1978

MATERIAL: 1,2-Dibromo-3-Chloropropane

SUBJECT: FINAL REPORT  
78-Week Toxicity and Carcinogenicity Study in Mice  
Project No. 174-125

#### SUMMARY

The test material, 1,2-dibromo-3-chloropropane (DBCP) was evaluated for carcinogenic potential and pharmacologic effects in male and female albino mice. DBCP was administered in the diet to three groups of animals (50/sex in each group) at levels of 0.3, 1.0, and 3.0 mg/kg of body weight per day for 78 weeks. An additional group of mice (50/sex) received the basal diet only and served as a control group.

Criteria evaluated for compound effect were mortality, clinical signs, food consumption, clinical laboratory data, and gross and microscopic pathology.

A dose-related increase in the incidences of stomach nodules was noted in all treated animals sacrificed at termination. Histological examinations of stomach sections from the control and high-dose group revealed the presence of chemically-induced neoplasia in 34 males and 24 females of the high-dose group. These neoplasms consisted of squamous cell papillomas and carcinomas in the nonglandular region of the stomach. Such neoplasms were not observed in stomach sections of control animals. Metastatic lesions from the primary gastric carcinomas were occasionally

noted in the liver, renal capsule, abdominal muscles, diaphragm, and other internal viscera. In addition to the neoplastic response, acanthosis, hyperkeratosis and increased basal cell activity of the gastric mucosa were apparent. These findings are attributed to the dietary administration of DBCP. Therefore, under the conditions of this study 1,2-dibromo-3-chloropropane is considered to be a carcinogen.

## INTRODUCTION

This study was designed to evaluate and characterize the carcinogenic potential and pharmacotoxic effects of 1,2-dibromo-3-chloropropane (DBCP) when administered in the diet to albino mice for 78 weeks. This study was initiated on June 28, 1976 and completed 78 weeks later on December 26, 1977. Terminal sacrifice of all animals was completed by January 13, 1978.<sup>a</sup> This final report presents the complete findings and interpretations of the entire study.

## TEST MATERIAL

The test material, 1,2-dibromo-3-chloropropane, (Fumazone F; AGR-133478) was received in a single shipment on February 7, 1975. The test material was a pale yellow liquid and considered to be composed of 100% active ingredient for dosage calculation purposes.

## TEST ANIMALS

Four hundred weanling albino mice (200/sex) of the HaM/ICR Swiss CD<sup>®</sup>-1 strain (received from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts) and approximately five to six weeks of age were employed in this study. The initial body weights for these mice ranged from 25 to 30 grams and 19 to 26 grams for the males and females, respectively.

<sup>a</sup> All animals were maintained on the appropriate diet until sacrificed.

## METHODS

Four hundred animals were randomized to obtain a homogeneous weight distribution and assigned to the following groups:

<u>Group</u>	<u>No. of Animals</u>		<u>Dietary Levels<sup>a</sup></u>	
	<u>Males</u>	<u>Females</u>	<u>Weeks 1-27</u> mg/kg/day	<u>Weeks 28-78</u> mg/kg/day
1 (Control)	50	50	0.0	0.0
2 (Low-dose)	50	50	0.3	0.6
3 (Mid-dose)	50	50	1.0	2.0
4 (High-dose)	50	50	3.0	6.0

<sup>a</sup> During Weeks 28 through 78 (inclusive) an error in calculating food consumption was made. A detailed explanation of this occurrence was documented by the Hazleton Laboratories Quality Assurance Unit and is presented in Appendix 6. The result of this error was the preparation of the diets based upon one-half of the actual food consumption. The dietary levels presented for Weeks 28 through 78 are true if the animals consumed the amount of feed as indicated in Table 1 for this period.

The mice were housed in polycarbonate boxes with filter tops in groups of five animals of the same sex and dosage level during Week 1 through Week 26. Heat treated Sani-Chips (Shurfire Products Corporation, Beltsville, Maryland) was used as bedding material. Both the bedding and boxes were changed twice weekly. All animals were housed individually in hanging wire mesh cages from Week 26 through termination. This change in protocol was necessitated due to fighting among the mice, predominantly males. Water and the appropriate diet were available ad libitum.

#### Diet Preparation and Administration

Because of the known volatility of DBCP, the stability of this material in the feed was determined in conjunction with a previously conducted long-term study in rats. These data indicated that approximately 40% of the test material was lost from the diet over a three-day period. To compensate for this loss, the test diets were overformulated by 40% such that the average daily compound consumption would approach the intended levels.

The appropriate amount of the test material was intimately mixed with a small amount of the basal laboratory diet, Purina® Laboratory Chow®. This premix was then added to the basal diet on a weight-per-weight basis and thoroughly mixed in a Patterson-Kelly twin shell blender. Fresh diets were prepared and presented twice weekly (on Mondays and Fridays), and were mixed according to the most recently recorded mean body weight and food consumption.

#### Observations and Records

All animals were observed daily for mortality and signs of morbidity. The following observations were made and recorded weekly from Weeks 0 through 12 and every four weeks from Weeks 16 through 78: individual body weights, food consumption, gross signs of systemic toxicity; and incidence, consistency, and location of all tissue masses.

### Clinical Laboratory Studies

#### Hematology:

The following determinations were performed on blood samples from five mice/sex/group at Weeks 13, 26, 52, and 77.

- Hematocrit (HCT)
- Hemoglobin (HGB)
- Erythrocyte Count (RBC)
- Erythrocyte Morphology
- Leukocyte Count (WBC)
- Differential Leukocyte Count

Blood samples for hematology parameters were obtained by segmental tail amputation.

#### Blood Chemistry

The following determinations were performed at termination.

- Serum Glutamic Oxaloacetic Transaminase (SGOT)
- Serum Glutamic Pyruvic Transaminase (SPGT)
- Alkaline Phosphatase (ALK PHOS)
- Blood Urea Nitrogen (BUN)
- Fasting Glucose
- Total Protein
- Plasma Cholinesterase (PLASMA CHE)
- Erythrocyte Cholinesterase (RBC CHE)
- Brain Cholinesterase (BRAIN CHE)

Blood samples from a sufficient number of animals were drawn so that at least 5 values/sex/group for each parameter could be obtained. Blood samples were taken by puncture of either the abdominal aorta or heart.

Methods for hematology and blood chemistry determinations are presented in Appendix 5.



### Analysis of Diet

Representative samples of the diet, prepared on the following dates were taken at 0, 24, 48, and 72 hours after mixing and analyzed for DBCP content:

August 30, 1976 - Week 8  
October 4, 1976 - Week 13  
January 3, 1977 - Week 26  
April 4, 1977 - Week 42  
June 27, 1977 - Week 50  
October 3, 1977 - Week 65  
December 19, 1977 - Week 76

Results of the diet analysis for DBCP content are presented in Appendix 3.

Methodology for DBCP Analysis: One gram samples of the diet were extracted once with a 3 ml aliquot of iso-propanol or propanol. Extraction was accomplished by agitation of the sample for one hour followed by centrifugation for 30 minutes. The resulting supernatant was decanted and an aliquot was injected into a gas chromatograph, fitted with an electron capture detector. The column was 2' x 1/8" (O.D.) stainless steel packed with 6% FFAP (Free Fatty Acid Phase) on Porapak Q, perfused with nitrogen (at 8.5 liters/minute) and held at 205°C.

### Terminal Studies

Sacrifice and Gross Pathology: After 78 weeks of treatment all surviving animals were sacrificed by exsanguination under sodium pentobarbital (Diabutal<sup>TM</sup>; Diamond Laboratories, Inc., Des Moines, Iowa). Necropsies were performed on all animals sacrificed by design at 78 weeks and all animals found dead or sacrificed in extremis during the course of study.

Tissue Preservation: From each mouse sacrificed by design, found dead or sacrificed in extremis, the following tissues were preserved in 10% neutral buffered formalin:

Brain	Pancreas
Thoracic Spinal Cord	Ovaries/Testes
Pituitary	Uterus
Thyroid	Prostate
Esophagus	Salivary Gland
Adrenals	Mesenteric Lymph Node
Heart	Urinary Bladder
Lung	Nerve with Muscle
Spleen	Eye
Liver	Bone Marrow
Kidney	Rib Junction
Stomach	Skin/Mammary Gland
Small Intestine	Unusual Lesions and
Large Intestine	Tissue Masses

### Histopathology

The following tissues from the control and high-dose animals were embedded in paraffin (Paraplast<sup>®</sup>), stained with hematoxylin and eosin and examined microscopically.

Kidneys	Testes
Liver	Palpable Tissues Masses
Stomach	Suspected Tumors

### Data Storage

All original data are presently stored at Hazleton Laboratories America, Inc.

Statistical Evaluation

The following data from the control and treated groups of the same sex were compared statistically: survival<sup>1</sup>, clinical laboratory data<sup>2,3,4</sup> and incidence of stomach nodules noted at necropsy<sup>5</sup>. All evaluations were conducted using the 5% probability level as the criterion for significance. Statistically significant results of the aforementioned tests are indicated throughout the tabulated data of this report in the following manner:

S- = Statistically significantly lower than control mean value.

S+ = Statistically significantly higher than control mean value.

- <sup>1</sup> Life Table. Sachs, R. 1959. Life table technique in the analysis of response - time data from laboratory experiments in animals Toxicol. Appl. Pharmacol. 1:203-227.
- <sup>2</sup> Test for Homogeneity of Variances. M.S. Bartlett. 1937. Some examples of statistical methods of research in agriculture and applied biology. J. Royal Statist. Soc. Suppl. 4:137-170.
- <sup>3</sup> One-Way Analysis of Variance. G.W. Snedecor and W.G. Cochran. 1967. one-way classifications. Analysis of variance. Pages 258-298 in Statistical Methods. Iowa State University Press, Ames, Iowa.
- <sup>4</sup> Method for Judging all Contrasts in Analysis of Variance. H. Scheffe. 1953. A method for judging all contrasts in the analysis of variance. Biometrika 40:87-104.
- <sup>5</sup> Chi-Square. Snedecor, G.W. and Cochran, W.G. 1967. Attribute data with more than one degree of freedom. Pages 228-257 in Statistical Methods. Iowa State University, Iowa.

## RESULTS

Mean Body Weights, Food Consumption and Survival (Table 1)

Evaluation of mean body weight, food consumption and survival data did not reveal any effects attributable to the administration of DBCP. The mean body weights of treated animals of both sexes were comparable at each interval during the study.

Statistical analysis of survival data revealed that survival was comparable between all treated and control groups except for the low-dose females in which survival was statistically significantly higher than the control group. Several accidental deaths (6) occurred during the study and are noted as such in Table 1. These deaths were not included in the analysis of survival data.

Food consumption data, presented in Table 1, are for group-housed animals during Weeks 0 through 24 and for individual animals during Weeks 28 through 78. Food consumption values increased after the animals were housed individually. This was probably due to feed spillage because the type of feeder was changed at that point. Food consumption data for treated animals were similar to control at each interval.

Compound Consumption (Table 1A)

Group mean compound consumption data are presented in Table 1A. Mean daily compound consumption for Weeks 1 through 24 and Weeks 29 through 78 are presented in Figure 1, page 12. Generally, compound consumption compares favorably with intended levels for the first 24 weeks. After Week 28, compound consumption approached twice the target level. This

change resulted from incorrect calculation of food consumption from Weeks 28 through termination, as presented on the following page in Figure 1. It should be noted, however, that since actual values for food consumption are overstated because of probable feed spillage, the actual compound consumed is probably less than that calculated between Weeks 28 through 78.

#### Analysis of Diet

Results of the analysis for DBCP content in the prepared diets are presented in Appendix 3.

Evaluation of these data revealed that at Weeks 8, 13, and 26, the "zero" hour concentration of DBCP, was comparable to the target level. At Week 65, the analysis revealed approximately twice the amount of DBCP present. The large variation in the data from week to week and in samples taken after "zero" hour is probably a reflection of the instability (high-volatility) of the test material.

#### Clinical Signs

No signs of compound-induced toxicity were observed throughout this 78-week study. The male mice in the control and high-dose groups were frequently observed fighting<sup>a</sup>. Consequently, sores, swelling, and alopecia involving the back, hind quarters, and tail were frequently noted. Other clinical signs noted with comparable frequencies between

<sup>a</sup> For this reason the male animals involved were separated into individual housing as of Week 16 (Groups 1, 2, and 3) and Week 5 (Group 4). All animals were individually housed after Weeks 26 through termination.

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Figure 1  
 Mean Daily Compound Consumption

Weeks 1-24

<u>Group 1</u>	<u>Target Level</u> mg/kg/day	<u>Actual Consumption</u>		<u>Percent Difference</u>	
		Male	Female	Male	Female
2	0.3	0.292	0.284	- 2.7	-5.3
3	1.0	0.884	0.948	-11.6	-5.2
4	3.0	2.896	2.903	- 3.5	-3.2

Weeks 28-78

<u>Group 1</u>	<u>Target Level</u> mg/kg/day	<u>Actual<sup>a</sup> Consumption</u>		<u>Percent Difference</u>	
		Male	Female	Male	Female
2	0.3	0.590	0.561	+96.7	+87.0
3	1.0	1.989	1.933	+98.9	+93.3
4	3.0	5.973	5.771	+99.1	+92.4

<sup>a</sup> These values are probably overstated because of feed spillage.

treated and control animals were thinness, urine stained fur, head tilt hyperactivity, and small, squinted, or lacrimating eyes.

#### Incidence of Palpable Nodules and Tissue Masses

The frequency of palpable nodules and tissue masses noted throughout this study at the designated intervals are presented by group in Table 4.

Generally, the incidence of nodules and tissue masses noted at each interval was comparable between treated and control animals.

#### Clinical Laboratory Studies

Hematology: Group mean values are presented in Table 2 and individual values are presented in Appendix 1.

Evaluation of the hematology data did not reveal any consistent statistical differences or dose-related patterns. A decreased hematocrit value, hemoglobin concentration, and red blood corpuscle population (significantly decreased) was noted in the high-dose males at Week 78. However, these differences resulted from two animals (Nos. 50302 and 50308) with low hemogram profiles.

Blood Chemistry: Group mean values are presented in Table 3 and individual data are presented in Appendix 2.

Evaluation of the blood chemistry data obtained at Week 78 did not reveal any findings considered to be related to DBCP administration. A large range of values for serum glutamic oxaloacetic transaminase, noted in treated groups of both sexes, is not uncommon for this age,

species, and strain. Evaluation of red blood corpuscles, plasma and brain cholinesterase data revealed no evidence of compound effect.

#### Gross Pathology

Gross pathology findings noted in those animals, sacrificed after 78 weeks of treatment are presented in Table 5. Gross pathology findings noted in those animals which died or were sacrificed in extremis are presented in Table 6.

Small, multiple, white nodules in the nonglandular mucosa of the stomach were frequently noted in treated animals sacrificed at termination. Statistical evaluation of this data revealed that the occurrence of these nodules was significantly higher in the treated groups as compared with controls. This finding is considered compound-related since the frequency of this finding (males Group 1, 0/28; Group 2, 13/26; Group 3, 24/28; Group 4, 26/26; females Group 1, 1/32; Group 2, 10/44; Group 3, 26/34; and Group 4, 38/38) follows a dose-related pattern. Other findings noted frequently in all groups involved complete or focal discoloration of the lungs, liver, pancreas and kidneys and enlargement of the mesenteric lymph node. In addition, both control and treated females were noted to have either ovarian cysts or the entire ovary encompassed with a watery cyst and distention of the uterine horns by cysts or nodules.

Findings frequently noted in animals which had died or were sacrificed in extremis consisted of complete or focal discoloration of the lungs, liver, and kidney; small multiple white nodules in the



nonglandular mucosa; enlargement of the mesenteric lymph node; and distention of the uterine horns accompanied by multiple cysts or nodules.

#### Histopathology

Individual histological findings noted in the examination of preserved tissues from all control and high-dose animals are presented in Appendix 4.

Chemically-induced neoplasia was present in stomach sections of both male (34/50) and female (24/50) high-dose treated mice. The neoplasms observed consisted of squamous cell papillomas and carcinomas in the nonglandular region of the stomach. Metastatic lesions from the primary gastric carcinomas were occasionally noted in the liver, involving the renal capsule, and involving the abdominal muscles and diaphragm and other internal viscera. In addition to the neoplastic response, acanthosis, hyperkeratosis, and increased basal cell activity of the gastric mucosa were apparent. A variety of spontaneously occurring neoplasms were observed in addition to the gastric carcinomas and a complete listing of tumor incidence is presented by group in Table 7.

Various spontaneous disease lesions and incidental findings were noted and consisted of the following: in the liver, microgranulomas were frequently noted along with amyloidosis, occasional perivascular lymphoid foci and congestion; kidney lesions consisted primarily of perivascular lymphoid foci, amyloidosis and minimal to moderate interstitial nephritis with occasional cortical cysts; primary renal neoplasms were not observed with the exception of a single treated male in which a renal tubule carcinoma was present.

Sections of the testes revealed a comparable incidence of spontaneous disease lesions and geriatric changes consisting of focal mineralization of seminiferous tubules along with occasional instances of unilateral and/or bilateral hypospermatogenesis. Unilateral aspermatogenesis was present in a treated male and bilateral aspermatogenesis was present in two control males and a single treated male.

In conclusion, microscopic evaluation of hematoxylin and eosin stained sections of liver, kidneys, stomach, testes, and unusual lesions from the control and high level mice revealed the presence of a tumorigenic effect in the nonglandular region of the stomach with the presence of squamous cell papillomas and carcinomas among the high level animals. Occasional instances of metastases of these lesions to other abdominal viscera were noted. Other treatment-related lesions consisted of acanthosis, hyperkeratosis and increased basal cell activity in the nonglandular region of the stomach. Spontaneous disease lesions and incidental findings were considered within normal limits for mice of this age and strain and were generally comparable between the control and high-dose treated mice.

#### Discussion

Inspection of the data indicate that during Weeks 28 through 78, the diets were incorrectly prepared. This was owing to mathematically incorrect food consumption values stemming from twice weekly preparation of the diet instead of the common weekly preparation. The consequence of this was that reported compound consumption values (Table 1A) were approximately twice their intended levels during Weeks 28 through 78. Retrospective

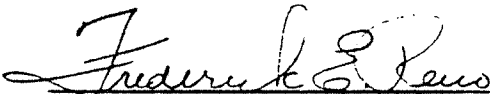
analysis demonstrates that the reported food consumption values for this sample period (see Table 1) approached twice the values recorded for the first 24 weeks for all groups. It is thought that a possible cause for this increase was feed spillage associated with the change in the type of feeder at Week 27, though there were no notations in the data regarding this. This in turn was required owing to the changes from group to individual housing due to the male mice fighting.

Therefore, inadvertently, actual compound consumption was probably not at the reported value (as stated in Table 1A) but closer to the intended values owing to spillage of the diet. This is not to say that there was not an error in diet preparation during Weeks 28 through 78, but that the spillage of the diet during this time (not uncommon in mice feeding studies) may have ameliorated the consequences of the error. In any event, this untoward occurrence did not negatively impact the final results of this study.

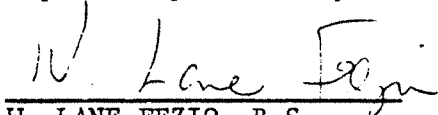
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Project No. 174-125

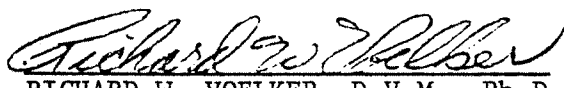
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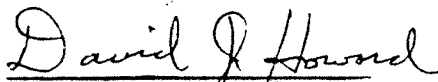
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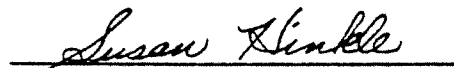
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TABLE 1  
MEAN BODY WEIGHTS, STANDARD DEVIATIONS, FOOD CONSUMPTION<sup>a</sup>, AND SURVIVAL DATA FOR MALE ANIMALS  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE

TIME INTERVAL WEEKS	GROUP 1				GROUP 2				GROUP 3				GROUP 4			
	BODY WEIGHT		BODY WEIGHT		BODY WEIGHT		BODY WEIGHT		BODY WEIGHT		BODY WEIGHT		BODY WEIGHT		BODY WEIGHT	
	MEAN	SI. DEV.	MEAN	SI. DEV.	MEAN	SI. DEV.	MEAN	SI. DEV.	MEAN	SI. DEV.	MEAN	SI. DEV.	MEAN	SI. DEV.	MEAN	SI. DEV.
	G.	G.	G.	G.	G.	G.	G.	G.	G.	G.	G.	G.	G.	G.	G.	G.
0	27	1.4	0	50/50	28	2.3	0	50/50	28	1.6	0	50/50	28	1.9	0	50/50
1	27	1.3	33	50/50	26	1.7	30	50/50	28	1.7	32	50/50	27	1.8	32	50/50
2	29	1.8	26	50/50	29	3.1	26	50/50	30	1.8	26	50/50	29	2.0	28	50/50
3	29	4.0	28	50/50	30	2.4	27	50/50	31	1.8	27	50/50	30	3.7	28	50/50
4	30	2.4	29	50/50	30	4.1	30	50/50	32	2.3	28	50/50	31	2.9	31	50/50
5	32	2.4	31	50/50	32	2.0	31	50/50	32	1.8	31	50/50	32	2.3	32 <sup>a</sup>	49/50
6	31	2.2	28	50/50	33	2.5	31	50/50	33	2.6	28	50/50	31	2.2	28 <sup>a</sup>	49/50
7	33	1.9	27	50/50	33	3.1	29	50/50	33	2.2	28	50/50	33	2.2	27 <sup>a</sup>	49/50
8	32	2.0	29	50/50	33	2.6	29	49/50	33	1.9	29	50/50	33	2.1	29 <sup>a</sup>	49/50
9	35	2.0	28	50/50	34	3.1	28	48/50	34	2.1	27	50/50	34	2.3	28 <sup>a</sup>	49/50
10	35	2.1	27	50/50	36	3.0	29	48/50	35	2.1	27	50/50	35	2.2	27 <sup>a</sup>	49/50
11	36	2.2	28	50/50	36	2.8	29	48/50	36	2.1	27	50/50	36	2.6	28 <sup>a</sup>	49/50
12	35	2.1	29	50/50	35	2.5	31	46/49 <sup>b</sup>	35	2.0	29	50/50	34	2.6	29 <sup>a</sup>	49/50
16	34	2.6	29 <sup>a</sup>	50/50	34	3.2	30 <sup>a</sup>	44/49	33	2.4	29 <sup>a</sup>	49/50	33	3.4	31 <sup>a</sup>	47/50
20	37	3.3	29 <sup>a</sup>	50/50	38	3.2	30 <sup>a</sup>	43/49	38	2.9	30 <sup>a</sup>	49/50	40	3.8	29 <sup>a</sup>	47/50
24	39	3.2	32 <sup>a</sup>	50/50	39	3.8	30 <sup>a</sup>	43/49	39	2.8	30 <sup>a</sup>	49/50	39	3.0	30 <sup>a</sup>	46/50
28c	39	2.3	54	50/50	39	3.5	53	43/49	38	2.5	49	49/50	37	2.7	73	45/50
32c	37	2.3	49	50/50	38	2.9	52	43/49	38	2.2	49	49/50	37	2.7	53	45/50
36c	39	2.7	45	49/50	40	2.8	43	43/49	39	2.4	42	48/50	39	2.5	44	45/50
40c	38	3.0	47	48/50	39	4.1	59	43/49	36	3.2	52	47/50	36	3.0	53	45/50
44c	39	3.9	42	47/50	38	3.0	46	42/49	39	2.8	43	47/50	40	2.8	47	45/50
48c	38	2.6	43	46/50	37	3.3	44	42/49	36	2.8	44	47/50	35	2.2	45	44/50
52c	40	2.8	43	45/50	39	3.1	45	42/49	38	2.6	37	46/50	39	2.5	44	44/50
56c	38	3.0	43	45/50	39	3.0	44	42/49	38	2.5	35	46/50	39	2.4	40	43/50
60c	38	3.0	37	44/50	39	3.3	42	41/49	38	2.2	39	43/50	39	3.1	38	41/50
64c	38	3.1	39	42/50	38	3.5	46	40/49	38	2.6	46	43/50	39	2.8	45	39/50
68c	38	2.8	48	41/50	38	4.1	43	39/49	39	3.8	44	42/50	37	2.8	48	36/50
72c	38	4.3	42	38/50	38	4.4	46	36/49	37	2.5	46	39/50	38	4.0	44	36/50
76c	39	3.8	40	34/50	39	3.8	48	33/49	39	5.7	42	35/50	39	3.0	40	28/50
78c	39	3.7	41	30/50	39	3.9	47	29/49	37	3.1	44	31/50	40	3.4	46	27/50

<sup>a</sup> Food consumption of animals separated out is not included in the mean. Beginning with Week 26, all animals were changed to individual housing.

<sup>b</sup> One animal died due to technical error.

<sup>c</sup> Food consumption data at this interval has been corrected for the error in the food consumption calculations. The correction was made by multiplying the original data by a factor of 2.

TABLE 1 - CONTINUED  
MEAN BODY WEIGHTS, STANDARD DEVIATIONS, FOOD CONSUMPTION<sup>a</sup>, AND SURVIVAL DATA FOR FEMALE ANIMALS  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE

TIME INTERVAL WEEKS	GROUP 1				GROUP 2				GROUP 3				GROUP 4			
	MEAN G.	SD G.	WEIGHT G.	FOOD G.	MEAN G.	SD G.	WEIGHT G.	FOOD G.	MEAN G.	SD G.	WEIGHT G.	FOOD G.	MEAN G.	SD G.	WEIGHT G.	FOOD G.
0	21	2.2	0	50/50	22	2.3	0	50/50	22	1.2	0	50/50	22	1.2	0	50/50
1	21	1.5	32	50/50	22	1.3	27	50/50	22	1.4	29	50/50	22	1.4	31	50/50
2	24	1.2	24	50/50	24	1.3	27	50/50	24	1.4	25	50/50	24	1.5	28	50/50
3	25	1.8	26	50/50	24	1.7	26	50/50	24	1.5	24	50/50	24	1.7	27	50/50
4	24	1.6	26	50/50	25	1.5	27	50/50	25	1.8	27	50/50	25	1.7	29	50/50
5	27	2.1	27	50/50	25	1.5	29	50/50	24	2.7	29	50/50	25	2.1	31	50/50
6	25	1.9	26	50/50	24	3.0	28	50/50	25	2.4	26	50/50	25	3.9	27	50/50
7	26	2.4	26	50/50	26	1.9	27	50/50	26	1.7	26	50/50	25	3.2	28	50/50
8	25	1.8	26	50/50	26	2.0	27	50/50	27	1.9	26	50/50	26	3.1	28	50/50
9	26	2.2	24	49/50	27	2.0	25	50/50	27	1.9	23	50/50	27	2.4	26	50/50
10	27	2.1	23	49/50	28	2.2	26	50/50	28	2.1	25	50/50	28	2.5	26	50/50
11	29	2.6	27	49/50	29	2.3	26	50/50	29	2.2	26	50/50	29	2.9	28	50/50
12	28	2.6	25	49/50	27	2.0	27	50/50	28	2.3	27	50/50	27	2.8	28	50/50
16	26	3.1	25	49/50	26	2.5	26	50/50	26	2.4	25	50/50	26	3.0	27	50/50
20	30	3.7	25	49/50	29	2.9	25	50/50	31	3.3	25	50/50	30	3.5	26	50/50
24	32	4.2	24	49/50	30	4.0	23	50/50	32	3.3	24	50/50	31	3.8	25	50/50
28c	31	2.8	51	49/50	31	2.3	55	50/50	31	2.8	56	50/50	31	2.9	54	50/50
32c	31	2.8	49	48/50	30	2.5	54	50/50	32	3.0	57	50/50	31	3.0	53	50/50
36c	33	3.2	46	48/50	32	2.7	42	50/50	32	3.0	46	49/50	32	3.5	56	50/50
40c	31	2.9	51	48/50	30	2.9	54	50/50	28	3.2	56	48/49 <sup>a</sup>	29	3.3	48	50/50
44c	31	3.9	50	44/47 <sup>b</sup>	32	2.9	45	50/50	33	3.4	46	48/49	34	3.8	48	50/50
48c	31	3.2	33	44/47	31	2.7	40	50/50	29	3.8	45	47/49	30	3.4	50	50/50
52c	33	2.8	43	44/47	33	2.7	40	50/50	33	3.0	43	47/49	33	3.3	44	50/50
56c	33	3.1	42	44/47	32	2.7	38	50/50	33	2.8	46	46/49	33	3.2	43	50/50
60c	33	3.1	42	44/47	32	2.9	43	50/50	33	3.1	44	43/49	33	3.8	42	50/50
64c	33	2.8	44	42/47	32	2.9	41	50/50	33	2.9	48	43/49	33	3.2	46	48/50
68c	33	3.0	43	41/47	32	3.1	45	50/50	32	2.9	47	43/49	32	3.4	43	46/50
72c	33	2.7	42	38/47	32	3.0	45	48/50	33	2.6	49	40/49	33	3.7	44	44/50
76	34	3.4	44	36/47	34	3.5	40	48/50	35	3.7	42	36/49	33	3.6	46	44/50
78	34	3.4	46	35/47	34	3.2	47	45/49 <sup>a</sup>	35	3.3	46	36/49	35	4.2	53	40/50

<sup>a</sup> One animal died due to a technical error.

<sup>b</sup> The death of three animals was attributed to lack of feed.

<sup>c</sup> Food consumption data at this interval has been corrected for the error in the food consumption calculations. The correction was made by multiplying the original data by a factor of 2.

Table 1A  
Mean Daily Compound Consumption<sup>a</sup>  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice

Time Interval Weeks	Males			
	Group 1	Group 2	Group 3	Group 4
	Compound Consumption mg/kg	Compound Consumption mg/kg	Compound Consumption mg/kg	Compound Consumption mg/kg
0	0.000	0.000	0.000	0.000
1	0.000	0.264	0.638	1.969
2	0.000	0.243	0.743	2.455
3	0.000	0.296	0.995	2.960
4	0.000	0.343	0.100	3.214
5	0.000	0.291	1.107	3.000
6	0.000	0.291	0.897	3.432
7	0.000	0.289	0.994	2.712
8	0.000	0.301	1.042	3.226
9	0.000	0.282	0.896	2.871
10	0.000	0.299	0.970	2.843
11	0.000	0.299	0.986	2.556
12	0.000	0.329	1.077	3.326
16	0.000	0.303	1.042	3.355
20	0.000	0.259	0.902	2.330
24	0.000	0.286	0.879	3.198
28 <sup>b</sup>	0.000	0.524	1.676	7.920
32	0.000	0.606	2.026	4.338
36	0.000	0.461	1.092	4.674
40	0.000	0.821	2.641	7.656
44	0.000	0.484	1.528	4.784
48	0.000	0.595	2.235	6.484
52	0.000	0.577	1.614	5.351
56	0.000	0.580	1.895	5.494
60	0.000	0.569	2.214	5.721
64	0.000	0.657	2.370	7.022
68	0.000	0.550	1.870	6.746
72	0.000	0.640	2.184	5.376
76	0.000	0.615	1.723	5.289
78	0.000	0.585	2.174	6.769

<sup>a</sup> In mg/kg of body weight per day.

<sup>b</sup> Values during Weeks 28 through 78 are probably greatly over-stated because of feed spillage.

Table 1A - Continued  
Mean Daily Compound Consumption<sup>a</sup>  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice

Time Interval Weeks	Females			
	Group 1	Group 2	Group 3	Group 4
	Compound Consumption mg/kg	Compound Consumption mg/kg	Compound Consumption mg/kg	Compound Consumption mg/kg
0	0.000	0.000	0.000	0.000
1	0.000	0.161	0.582	1.868
2	0.000	0.273	0.789	2.467
3	0.000	0.294	0.986	2.909
4	0.000	0.309	1.080	3.099
5	0.000	0.315	1.036	3.189
6	0.000	0.302	0.891	2.669
7	0.000	0.267	0.971	3.104
8	0.000	0.297	0.977	3.015
9	0.000	0.265	0.998	2.999
10	0.000	0.305	0.982	3.051
11	0.000	0.295	0.986	2.993
12	0.000	0.301	0.992	3.081
16	0.000	0.286	0.975	2.997
20	0.000	0.296	1.002	3.046
24 <sup>b</sup>	0.000	0.296	0.975	3.053
28	0.000	0.583	1.987	5.972
32	0.000	0.429	2.101	6.106
36	0.000	0.600	2.012	5.950
40	0.000	0.591	2.000	5.935
44	0.000	0.583	2.031	6.030
48	0.000	0.590	1.951	5.905
52	0.000	0.589	1.992	5.981
56	0.000	0.594	1.991	6.050
60	0.000	0.595	1.962	5.927
64	0.000	0.604	2.036	5.914
68	0.000	0.623	2.014	5.970
72	0.000	0.583	2.015	6.019
76	0.000	0.588	1.971	6.054
78	0.000	0.296	0.995	2.985

<sup>a</sup> In mg/kg of body weight per day.

<sup>b</sup> Values during Weeks 28 through 78 are probably greatly over-stated because of feed spillage.



Table 2  
Mean Hematology Values<sup>a</sup>  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice

Group Dose Level	Hematocrit (%)				Hemoglobin (mg/dl)				
	Week				Week				
	13	26	52	78	13	26	52	78	
Male									
1 0.0 mg/kg	Mean	48.20	50.00	45.40	43.90	16.74	16.08	15.40	14.56
	S.D.	1.79	1.27	2.97	2.84	1.07	0.66	0.73	1.05
2 0.3 mg/kg	Mean	48.00	49.40	46.20	43.60	16.48	16.14	15.06	13.54
	S.D.	1.27	1.67	2.77	3.31	0.33	0.58	1.22	1.54
3 1.0 mg/kg	Mean	47.60	49.80	44.40	45.10	15.60	16.46	15.10	13.36
	S.D.	4.83	0.84	1.52	4.07	2.03	0.40	0.28	2.00
4 3.0 mg/kg	Mean	48.60	49.30	45.20	39.40	15.36	16.32	13.88	11.10
	S.D.	1.67	0.97	3.03	7.36	0.97	0.99	1.51	3.26
Female									
1 0.0 mg/kg	Mean	51.40	50.30	50.00	44.10	17.34	16.52	15.02	13.38
	S.D.	1.52	1.86	1.87	3.27	0.60	0.95	0.98	1.20
2 0.3 mg/kg	Mean	50.80	50.40	47.00	42.60	16.60	16.60	15.00	13.82
	S.D.	2.77	2.63	2.83	3.78	0.67	0.68	1.23	1.61
3 1.0 mg/kg	Mean	51.80	52.10	50.40	44.90	16.16	16.50	14.68	12.58
	S.D.	2.59	3.85	2.88	6.98	0.48	0.89	0.79	2.06
4 3.0 mg/kg	Mean	50.80	50.20	49.00	45.00	16.76	16.18	15.62	13.24
	S.D.	1.30	1.79	1.58	3.79	1.06	0.54	0.73	1.34

<sup>a</sup> Based on five animals/sex/group.

Table 2 - Continued<sup>a</sup>  
Mean Hematology Values<sup>a</sup>  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice

Group Dose Level	Erythrocyte Count ( $\times 10^6/\text{mm}^3$ )				Leukocyte Count ( $\times 10^3/\text{mm}^3$ )			
	Week				Week			
	13	26	52	78	13	26	52	78
Male								
1	Mean	8.244	8.416	9.070	10.100			
0.0 mg/kg	S.D.	2.218	0.234	0.581	0.936	12.34	12.02	12.92
						4.26	4.50	1.33
								13.16
2	Mean	9.572	8.970	9.078	9.044	14.94	17.86	19.46
0.3 mg/kg	S.D.	0.745	0.610	0.801	0.890	3.39	6.17	5.91
								14.12
								7.57
3	Mean	9.222	8.546	8.884	8.952	S <sup>+</sup>		
1.0 mg/kg	S.D.	1.269	0.539	0.547	0.667	25.10	15.24	18.20
						5.60	6.75	3.72
								16.56
4	Mean	9.430	8.830	8.772	7.288 <sup>S-</sup>	14.32	17.54	19.98
3.0 mg/kg	S.D.	0.282	0.515	0.851	2.031	6.10	3.72	8.01
								31.34 <sup>b</sup>
								17.50
Female								
1	Mean	10.230	9.182	9.466	8.850	25.10	7.78	16.32
0.0 mg/kg	S.D.	0.748	0.556	0.819	0.992	3.53	1.03	2.49
								16.30
2	Mean	10.156	9.080	9.390	9.038	18.66	6.84	11.00
0.3 mg/kg	S.D.	0.689	0.489	0.713	1.052	2.13	1.99	6.68
								13.22
3	Mean	10.630	9.614	9.346	8.638	17.72 <sup>S+</sup>	15.68 <sup>S+</sup>	14.74
1.0 mg/kg	S.D.	0.649	0.738	0.908	1.298	3.68	5.14	2.11
								11.12
								2.07
4	Mean	10.422	8.900	9.166	8.906	19.30	10.26	13.80
3.0 mg/kg	S.D.	0.835	0.376	0.180	0.679	4.03	2.87	2.95
								14.24
								4.92

<sup>a</sup> Based on five animals/sex/group.

<sup>b</sup> Includes elevated values of 40.7 and 55.5 for two animals.

Table 3  
Mean Clinical Chemistry Values  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Week 78

Group Dose Level	SCOT IU/L	SGPT IU/L	ALK PHOS IU/L	BUN mg/dl	Fasting Glucose g/dl	Total Protein mg/dl	RBC CHE <sup>a</sup> Aph/min	Plasma CHE <sup>a</sup> Aph/min	Brain CHE <sup>a</sup> Aph/min
Males									
1	Mean	11.2	27.00	68.80	93.6	4.10	0.573	2.311	3.141
0.0 mg/kg	S.D. n	6.1 8	4.55 7	25.34 7	13.1 5	0.40 8	0.103 5	0.065 5	0.382 5
2	Mean	10.0	30.83	71.63	104.2	4.56	0.486	2.305	3.311
0.3 mg/kg	S.D. n	2.8 7	10.80 6	15.99 6	20.9 5	0.47 7	0.059 5	0.065 5	0.446 5
3	Mean	21.9	55.29	60.86	71.2	4.33	0.480	2.299	3.082
1.0 mg/kg	S.D. n	24.5 7	36.39 7	30.08 6	22.4 4	0.40 7	0.128 5	0.077 5	0.386 5
4	Mean	18.1	35.00	45.05	90.5	4.54	0.514	2.255	2.935
3.0 mg/kg	S.D. n	8.5 8	31.88 6	9.32 6	42.9 4	0.63 8	0.032 5	0.062 5	0.174 5
Females									
1	Mean	12.0	44.83	64.70	55.0	4.40	0.631	2.320	2.888
0.0 mg/kg	S.D. n	3.9 6	18.43 6	14.43 6	31.3 2	0.40 5	0.102 5	0.025 5	0.507 5
2	Mean	16.5	77.71	59.81	81.3	4.77	0.733	2.303	3.122
0.3 mg/kg	S.D. n	8.5 7	34.32 7	28.63 7	20.1 3	0.71 7	0.161 5	0.035 5	0.269 5
3	Mean	14.3	48.43	68.99	90.6	4.61	0.631	2.351	2.790
1.0 mg/kg	S.D. n	8.8 7	18.88 7	28.74 7	19.0 4	0.39 7	0.156 5	0.025 5	0.178 5
4	Mean	19.2	65.80	54.58	91.2	4.28	0.686	2.375	2.517
3.0 mg/kg	S.D. n	7.5 6	19.75 5	24.33 5	25.7 5	0.62 6	0.159 5	0.074 5	0.371 5

<sup>a</sup> Samples were taken at Week 80.

Table 4  
Incidence of Palpable Nodules, Tissue Masses, and Wart-Like Lesions<sup>a</sup>  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice

Group Dose Level	Weeks																					
	5	6	11	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	78	
Males																						
1 Control	0/50	0/50	0/50	0/50	8/50	2/50	1/50	3/50	6/50	1/49	6/48	5/47	5/46	7/45	10/45	1/44	1/42	5/41	4/38	2/34	2/30	
2 0.3 mg/kg	0/50	0/50	0/48	1/46	3/44	3/43	0/43	1/43	1/43	3/43	2/43	4/42	5/42	3/42	3/42	1/41	1/40	9/39	15/36	9/33	7/29	
3 1.0 mg/kg	0/50	0/50	0/50	0/50	1/49	1/43	1/49	2/49	6/49	3/48	10/47	10/47	8/47	6/46	6/46	4/43	3/43	7/42	4/39	5/35	5/31	
4 3.0 mg/kg	1/49	1/49	1/49	1/49	3/47	0/47	0/46	1/45	3/45	1/45	7/45	8/45	7/44	7/44	7/43	2/41	2/39	4/36	5/36	4/28	4/27	
Females																						
1 Control	0/49	0/49	0/49	0/49	0/49	0/49	0/49	0/49	0/48	0/48	0/48	1/44	0/44	0/44	0/44	0/44	0/42	1/41	1/36	1/36	1/35	
2 0.3 mg/kg	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/48	2/48	1/45	
3 1.0 mg/kg	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/49	0/48	0/48	0/47	1/47	1/46	1/43	1/43	1/43	1/40	1/36	1/36	
4 3.0 mg/kg	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/48	2/46	1/44	1/44	0/40	

<sup>a</sup> The number of animals with a finding out of the total number of animals observed is presented. Only those intervals at which nodules, tissue masses, or wart-like lesions were noted are presented.

### Gross Pathology Findings

DESCRIPTION OF FINDINGS	Dose Level - mg/kg:		Group: Sex:		1		2		3		4	
			0.0		0.3		1.0		3.0			
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Number of Animals Examined	28	32	26	44	28	34	26	38				
Number of Animals with No Gross Findings	10	1	3	2								
PITUITARY												
Raised Area on Surface												1
LUNG												
Mottled	1	4	3	2	1	2	1	2				
Focal Lesions			1	1								
Pale		2										
Cystic Areas		2										
White Foci												
Gray Foci		1		1		1	1	1			1	1
Red Foci												27
Lobe(s) Consolidated		1		1	1	1	1	1			1	2
With Nodules											1	2
Lobe Adhering to Ribs				1	1		1					
HEART												
Surrounded by Yellow Globules			1									
LIVER												
Lobe Consolidated				1							1	
Friable												
With Cysts or Nodules	2	2	1	2		3	1	5				
Yellow Tinge	1			1		1						
Yellow Foci	2	1	2	3		1	1	3				
Tan Colored												
Dark Colored	1						1					
Pale				1								
White Foci	1	1	1			1		1			1	1
Indented Areas												
White Nodule	1											
Tissue Mass, 1.6 x 1.3 x 1.1 cm												
Tissue Mass, Brown, 2.5 x 2.0 cm			1									1

Table 5 - Continued  
Gross Pathology Findings  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Animals Sacrificed at Termination

DESCRIPTION OF FINDINGS	Dose Level - mg/kg:		Group:		2		3		4	
	0.0		1		0.3		1.0		3.0	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
SPLEEN										
Enlarged			2				2		3	
Small							1		1	
Thickened			1					1		
Irregular Shape					1					
Mottled					1		1		3	1
Rough Surface							1			
Pale									1	
Dark Coloration							1			
With Yellow Nodules					1					
KIDNEYS										
Pale	1		2				2		1	
Mottled			1							28
Fatty Area	1									
Cystic Areas	1		3		1	1			1	2
Yellow Foci					1				1	
Indented Area					2					
Dark Coloration							1		1	
Cortex - Rough										
Pelves - Contain Granules							1		1	
- Dilated			1							1
With Tissue Mass					2	1				
ADRENALS										
Pale	2									
STOMACH										
Small Multiple White Nodules in the Nonglandular Area			1		13	10	24	26	26	38
Dark Red Area					1					

Table 5 - Continued  
Gross Pathology Findings  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Animals Sacrificed at Termination

DESCRIPTION OF FINDINGS	Dose Level - mg/kg:		Group:		1		2		3		4	
			Sex:		0.0		0.3		1.0		3.0	
			Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
PANCREAS												
Yellow Foci			1		1		3		1		3	
White Foci					1		1					1
Enlarged			1									
Dark Coloration												
With Nodules or Cysts			1	1					1	1		
SMALL INTESTINES												
Distended			2	1	1				1		1	
URINARY BLADDER												
Walls Thickened					1							
Lining Containing Cysts					1							
TESTES												
Small			1						1			
Gray												
Dark Coloration											1	1
SEMINAL VESICLES												
Enlarged			3									
White			2									
With Nodules			1									
PROSTATE												
Enlarged			1						1		1	
OVARY												
Surrounded by a Watery Cyst					7		10					10
Having Cysts					9		8		13			8
Enlarged					2				7			

Table 5 - Continued  
 Gross Pathology Findings  
 78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
 Animals Sacrificed at Termination

DESCRIPTION OF FINDINGS	Group: 1		2		3		4	
	Dose Level - mg/kg:		0.3		1.0		3.0	
	Sex: Male	Female	Male	Female	Male	Female	Male	Female
UTERUS								
Distended		1						4
Walls Thickened		1						3
UTERINE HORNS								
Distended		15	23		19			10
Tortuous		1	9					1
Walls Thickened		7	10		5			8
With Nodules or Cysts		12	26		20			21
Tissue Mass, Red		2						1
LYMPH NODES								
Mesenteric - Discolored	1	1	2		1		1	
- Enlarged	2	9	8		4		4	
Bronchial - Enlarged				1				1
Cervical - Enlarged			3				1	
- Pale								1
- With Tissue Mass, Pale Yellow						1		
Axillary - Enlarged						1		
Abdominal - Enlarged		1						1
Pancreatic - Enlarged		1						
Thoracic - Enlarged								1
Sublumbar - Enlarged	1			1		1		3
- With Tan Nodule				1				
SALIVARY GLAND								
Enlarged								
With Nodules								1
INGUINAL HERNIA							1	



Table 5 - Continued  
 Gross Pathology Findings  
 78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
 Animals Sacrificed at Termination

DESCRIPTION OF FINDINGS	Dose Level - mg/kg:	Group:		2		3		4	
		1		0.3		1.0		3.0	
		Male	Female	Male	Female	Male	Female	Male	Female
THORACIC CAVITY									
Contains Reddish Fluid		1							
Contains Clear Fluid									1
ABDOMINAL CAVITY									
Contains Reddish Fluid		1				1			1
Contains Clear Fluid									
Dark Blue Tissue Mass, 1.3 x 1.0 x 0.3 cm						1			
ESOPHAGUS									
Nodule 2 mm diameter	1								
ANUS									
Tissue Mass, with Pockets of Yellow Fluid						1			
SKELETAL MUSCLE									
Tissue Mass, Involving Muscle of Back						1			

Table 6  
Gross Pathology Findings  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Animals Found Dead or Sacrificed in Extremis

DESCRIPTION OF FINDINGS	Dose Level - mg/kg:		Group:		1		2		3		4	
	Sex:		mg/kg:		0.0		0.3		1.0		3.0	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Number of Animals Examined	22	18	24	6	22	16	24	12	24	12		
Number of Animals with No Gross Pathology <sup>a</sup>	1			1								
Number of Animals with Advanced Autolysis <sup>a</sup>		3	1	1		1		2				
Number of Accidental Deaths <sup>a</sup>												
BRAIN												
Soft		2	1		1	1						
EYE												
Opaque		1				1						
THYMUS												
Enlarged	2				1	1						
LUNGS												
Dark Coloration	2	3	2			1						
Dark Foci	5	3	4			4						
Mottled	5	1	4			1						
Pale Coloration	1		1			1						
Consolidated Lobe(s)	1	1		1		1						
Bright Red												
Congested			1			1						
Adhered to Diaphragm			1									
With Nodules												
HEART												
Dark Coloration												
Pale Coloration		1										

<sup>a</sup> Findings from animals killed by accident or with advanced autolysis were not included.

Table 6 - Continued  
Gross Pathology Findings  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Animals Found Dead or Sacrificed in Extremis

[illegible]

Table 6 - Continued  
 Gross Pathology Findings  
 78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
 Animals Found Dead or Sacrificed in Extremis

DESCRIPTION OF FINDINGS	Group:		Dose Level - mg/kg:		1		2		3		4	
	Sex:		mg/kg:		0.0		0.3		1.0		3.0	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
KIDNEY												
Dark Coloration	2	1	5						2		1	
Mottled	3	2	2							3	1	
Pale	3	3	4						3	3	6	4
Cysts on Surface	2										2	
Rough or Pitted Surface	3	1	2						2	1	2	1
Enlarged			1									
Ureters - Distended	1		2						3	1	2	1
Pelvis - Dilated	3											
- Eroded	1								1			
Cortex - Pitted												
Tissue Mass with Red Foci 1.5 x 1.5 x 1.0 cm			1									
ADRENALS												
Enlarged												
With White Nodule											1	
STOMACH												
Dark Material on Lining	2	1	1						3		1	3
White Nodules on Lining of Nonglandular Area			3						4	4	7	5
Lining Smooth			3									
Walls Thickened											1	
PANCREAS												
Dark Area(s)	2											1
Enlarged	1								3	1		
With Nodules or Cysts		1							1		1	
SMALL INTESTINE												
Distended	3	4	7						3	1	1	4
Filled with Fluid or Gas	2	2										1
Discolored		3	1						1	1	1	
Contains Gelatinous Material			1						1			
Soft									2	1		2

1 34 1

Table 6 - Continued  
 Gross Pathology Findings  
 78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
 Animals Found Dead or Sacrificed in Extremis

DESCRIPTION OF FINDINGS	Dose Level - mg/kg:		Group:		1		2		3		4	
	Sex:		mg/kg:		0.0		0.3		1.0		3.0	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
EPIDIDYMS												
Enlarged	1											
DUCTUS DEFERENS												
Enlarged	1											
OVARIES												
Surrounded by a Watery Cyst			2				1		1		1	
Have Multiple Cysts			1				1					
Enlarged											1	
Tissue Mass 1.5 x 1.5 x 1.0 cm			1									
UTERUS												
Distended			2						3		3	
Tissue Mass, Red									1			
UTERINE HORNS												
Distended			3				2		2		3	
Having Multiple Cysts			2				2		5		5	
Walls Thickened			1				1		3		1	
Tortuous			1						2		2	
PREPUTIAL GLANDS												
Enlarged	4								1			
Containing Greenish Material									1			
THORACIC CAVITY												
Containing Clear Fluid	1		1				1		1		1	
Containing Dark Fluid	2		2						3		1	

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Table 6 - Continued  
Gross Pathology Findings  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Animals Found Dead or Sacrificed in Extremis

DESCRIPTION OF FINDINGS	Group:		Dose Level - mg/kg:		1		2		3		4	
	Sex:		mg/kg:		0.0		0.3		1.0		3.0	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
LYMPH NODES												
Mesenteric - Enlarged	4		4				1		5		2	3
- Dark	3						1		3		2	3
- Gelatinous		1										
- Gray							1					
Cervical - Enlarged				1					1	1	1	
Bronchial - Enlarged										1		
Abdominal - Enlarged	3								1			
Thoracic - Enlarged												
Axillary - Enlarged	1						3					
Inguinal - Enlarged							1					
Sublumbar - Enlarged										1	1	
All Nodes - Enlarged and Firm											1	36
URINARY BLADDER												
Distended	4						2				4	
With Crystals							1				1	
Walls Thickened							1		2		1	
Filled with Dark Fluid							1		1		1	
With Cysts in Lining									1			
TESTES												
Small											1	
Discolored							2				1	
PROSTATE												
Enlarged											1	
SEMINAL VESICLES												
Enlarged	1								1		1	
Cystic							1				1	
Dark Coloration							1		1			

Table 6 - Continued  
 Gross Pathology Findings  
 78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
 Animals Found Dead or Sacrificed in Extremis

DESCRIPTION OF FINDINGS	Dose Level - mg/kg:		Group:		1		2		3		4	
			Sex:		0.0		0.3		1.0		3.0	
			Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
ABDOMINAL CAVITY												
Containing Clear Fluid			2						1			
Containing Dark Fluid			2	3		1		4				2
CAECUM												
Distended											1	
Discolored			1									
VENTRAL MUSCLE AND SKIN EDEMIC					2	4	1		1			1
SUBCUTANEOUS GELATINOUS MATERIAL					1	1			6	2		1
ALL TISSUES DARK					1				1		2	1
ANUS												1
Nodule, Filled with Gelatinous Material 1.5 x 1.5 x 1.5 cm						1						1
TISSUE MASSES												
Involving Leg, firm Tan Colored, 3.5 x 2.5 x 2.5 cm							1					
Inguinal Area, Firm, Tan 2 x 2 x 0.5 cm							1					
Along Backbone							1					
Involving, Base of Tail and Rectum												1
Involving Hind Leg Muscle 8 x 6 x 6 mm												1

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Table 7

Incidence of Histologically Proven Neoplasms  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice

ORGAN AND DESCRIPTION	Group 1		Group 4	
	Males	Females	Males	Females
PITUITARY				
Adenoma				1
ADRENAL				
Metastatic Squamous Cell Carcinoma			1	
Pheochromocytoma				1
LUNG				
Alveolar/Bronchiolar Adenoma				3
Alveolar/Bronchiolar Carcinoma				1
SPLEEN				
Hemangiosarcoma		1		
Metastatic Squamous Cell Carcinoma			1	
LIVER				
Hepatocellular Adenoma	2		1	1
Hepatocellular Carcinoma				1
Metastatic Squamous Cell Carcinoma			4	1
KIDNEY				
Renal Tubule Carcinoma			1	
Metastatic Squamous Cell Carcinoma			1	
Renal Tubule Hyperplasia		1		
STOMACH				
Squamous Cell Papilloma			6	6*
Squamous Cell Carcinoma			26	19
ABDOMINAL MUSCLE & DIAPHRAGM				
Squamous Cell Carcinoma Metastatic			3	
PANCREAS				
Squamous Cell Carcinoma Metastatic			1	

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\* Mouse No. 50360 had papilloma and carcinoma.



Table 7 - Continued  
Incidence of Histologically Proven Neoplasms  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice

ORGAN AND DESCRIPTION	Group 1		Group 4	
	Males	Females	Males	Females
UTERUS				
Fibrosarcoma				1
Endometrial Stromal Polyp				1
MESENTERIC LYMPH NODE				
Metastatic Squamous Cell Carcinoma			2	
UNUSUAL LESIONS				
Mammary Gland Adenocarcinoma				1
Fibrosarcoma				1
HEMATOPOIETIC NEOPLASMS				
Malignant Lymphoma (Stem Cell)			1	
Malignant Lymphoma (Histiocytic)		1		

APPENDIX 1  
INDIVIDUAL & MEAN HEMATOLOGY VALUES  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE

MALE - WEEK 13

GROUP NO AND DOSE LVL	ANIMAL NUMBER	HCT %	HGB G/DL	RBC MILLS	WBC THS	DIFFERENTIAL							BAND %	SEG %	LYMPH %	MONO %	EOSIN %	BASO %
						BLAST %	META %	BAND %	SEG %									
1 0.0 MG/KG	50001	47.0	15.6	4.35	16.7	0	0	0	0	0	0	13	84	0	3	0		
	50002	50.0	17.4	9.69	17.2	0	0	0	0	0	15	80	0	4	0			
	50003	48.0	17.2	9.36	10.3	0	0	0	0	0	20	77	0	2	0			
	50004	46.0	15.6	8.53	8.9	0	0	0	0	0	29	69	0	2	0			
	50005	50.0	17.9	9.29	8.6	0	0	0	0	0	16	77	0	0	0			
	MEAN	48.20	16.74	8.244	12.34													
	S.D.	1.79	1.07	2.218	4.26													
2 0.3 MG/KG	50101	47.0	16.3	8.93	19.1	0	0	2	9	87	0	2	0	0	2	0		
	50103	49.5	16.5	9.53	16.1	0	0	0	27	70	0	2	1	0	1	0		
	50104	49.0	17.0	10.82	10.7	0	0	0	28	69	0	1	2	0	2	0		
	50105	46.5	16.5	9.50	12.3	0	0	0	17	79	0	3	1	0	1	0		
	50106	48.0	16.1	9.08	16.5	0	0	1	10	83	0	5	1	0	1	0		
	MEAN	48.00	16.48	9.572	14.94													
	S.D.	1.27	0.33	0.745	3.39													
3 1.0 MG/KG	50201	50.0	17.4	10.89	23.0	0	0	0	37	58	3	13	2	0	2	0		
	50202	52.0	16.1	8.37	27.8	0	0	0	60	27	0	9	0	0	0	0		
	50203	51.0	17.0	10.22	20.4	0	0	0	32	59	0	2	0	0	0	0		
	50204	44.0	15.2	8.70	20.7	0	0	0	62	35	0	2	1	0	0	0		
	50205	41.0	12.3	7.93	33.6	0	0	2	52	41	0	5	0	0	0	0		
	MEAN	47.60	15.60	9.222	25.10 <sup>st</sup>													
	S.D.	4.83	2.03	1.269	5.60													
4 3.0 MG/KG	50302	50.0	14.8	9.50	13.2	0	0	0	23	72	1	10	4	0	0	0		
	50303	50.0	16.5	9.83	19.6	0	0	0	19	80	0	5	1	0	0	0		
	50304	46.0	14.8	9.08	5.5	0	0	2	24	68	0	1	1	0	0	0		
	50305	49.0	14.4	9.26	20.6	0	0	1	29	68	0	1	1	0	0	0		
	50306	48.0	16.3	9.48	12.7	0	0	0	36	64	0	0	0	0	0	0		
	MEAN	48.60	15.36	9.430	14.32													
	S.D.	1.67	0.97	0.282	6.16													

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APPENDIX 1 - CONTINUED  
INDIVIDUAL & MEAN HEMATOLOGY VALUES  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE

FEMALE - WEEK 13

GROUP NO AND DOSE LVL	ANIMAL NUMBER	HCT %	HGB G/DL	RBC MILLS	WBC THS	DIFFERENTIAL							BASO %
						BLAST %	META %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %	
1 0.0 MG/KG	50051	53.0	17.4	9.94	28.5	0	0	0	20	76	2	2	0
	50052	52.0	17.9	11.40	28.6	0	0	0	16	84	0	0	0
	50053	49.0	17.0	9.61	24.9	0	0	0	26	73	1	0	0
	50054	52.0	17.9	10.53	20.4	0	0	0	17	83	0	0	0
	50055	51.0	16.5	9.67	23.1	0	0	0	26	68	2	4	0
	MEAN	51.40	17.34	10.230	25.10								
	S.D.	1.52	0.60	0.748	3.53								
2 0.3 MG/KG	50151	55.0	17.4	10.82	22.2	0	0	2	50	45	2	1	0
	50152	49.0	17.0	9.87	17.9	0	0	2	23	72	3	0	0
	50153	50.0	16.5	10.00	16.5	0	0	0	43	54	0	3	0
	50154	48.0	16.5	9.23	18.1	0	0	0	30	66	2	0	0
	50155	52.0	15.6	10.86	18.6	0	0	0	28	72	0	0	0
	MEAN	50.80	16.69	10.156	18.66								
	S.D.	2.77	0.67	0.689	2.13								
3 1.0 MG/KG	50251	49.0	16.7	9.92	24.0	0	0	0	29	63	2	6	0
	50252	55.0	15.4	10.24	18.0	0	0	2	30	66	2	0	0
	50253	50.0	16.3	10.54	15.1	0	0	0	30	63	3	4	0
	50254	54.0	16.3	11.62	15.8	0	0	0	26	67	7	0	0
	50255	51.0	16.1	10.83	15.7	0	0	1	44	55	0	0	0
	MEAN	51.80	16.16	10.630	17.72								
	S.D.	2.59	0.48	0.649	3.68								
4 3.0 MG/KG	50351	53.0	18.4	10.59	25.6	0	0	0	31	67	1	1	0
	50352	50.0	16.1	10.45	17.6	0	0	1	23	73	2	1	0
	50353	50.0	15.6	9.39	15.4	0	0	0	18	81	1	0	0
	50354	51.0	17.0	10.02	17.1	0	0	0	18	82	0	0	0
	50355	50.0	16.7	11.66	20.8	0	0	0	26	73	1	0	0
	MEAN	50.80	16.76	10.422	19.30								
	S.D.	1.30	1.06	0.835	4.03								

APPENDIX 1 - CONTINUED  
INDIVIDUAL & MEAN HEMATOLOGY VALUES  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE

MALE - WEEK 26

GROUP NO AND DOSE LVL	ANIMAL NUMBER	HCT %	HGB G/DL	RBC MILLS	WBC THS	DIFFERENTIAL						BASO %	
						BLAST %	META %	BAND %	SEG %	LYMPH %	MONO %		EOSIN %
1 0.0 MG/KG	50001	49.0	15.3	8.64	19.1	0	0	3	40	55	0	2	0
	50002	50.0	15.8	8.12	13.2	0	0	0	29	69	1	1	0
	50003	51.0	16.0	8.55	7.2	0	0	1	77	21	0	1	0
	50004	48.5	16.2	8.21	10.0	0	0	0	25	72	0	3	0
	50005	51.5	17.1	8.56	10.6	0	0	0	37	61	0	2	0
	MEAN S.D.	50.99 1.27	16.08 0.66	8.416 0.234	12.02 4.50								
2 0.3MG/KG	50101	49.5	16.2	9.02	18.5	0	0	1	32	62	1	4	0
	50103	49.5	16.0	9.00	21.9	0	0	0	50	47	0	3	0
	50104	52.0	17.1	9.82	7.1	0	0	0	38	62	0	0	0
	50105	47.5	15.6	8.91	20.1	0	0	0	22	78	0	0	0
	50106	48.5	15.8	8.10	21.7	0	0	2	44	53	1	0	0
	MEAN S.D.	49.40 1.67	16.14 0.58	8.970 0.610	17.86 6.17								
3 1.0 MG/KG	50201	49.0	17.1	8.91	10.1	0	0	3	25	72	0	0	0
	50202	49.0	16.2	8.56	23.7	0	0	2	66	32	0	0	0
	50203	50.0	16.6	8.42	20.5	0	0	2	62	36	0	0	0
	50204	50.0	16.2	7.72	14.1	0	0	4	26	66	0	4	0
	50205	51.0	16.2	9.12	17.8	0	0	7	34	57	2	0	0
	MEAN S.D.	49.80 0.84	16.46 0.40	8.546 0.539	15.24 6.75								
4 3.0 MG/KG	50302	48.0	16.2	8.51	19.6	0	0	4	22	74	0	0	0
	50303	50.0	17.4	8.74	14.8	0	0	1	40	53	4	2	0
	50304	49.0	16.0	9.70	22.8	0	0	5	35	56	0	4	0
	50305	49.0	14.9	8.39	16.9	0	0	7	61	28	0	4	0
	50306	50.5	17.1	8.81	13.6	0	0	0	34	62	0	4	0
	MEAN S.D.	49.30 0.97	16.32 0.99	8.830 0.515	17.54 3.72								

APPENDIX 1 - CONTINUED  
INDIVIDUAL & MEAN HEMATOLOGY VALUES  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE

FEMALE - WEEK 26

GROUP NO AND DOSE LVL	ANIMAL NUMBER	HCT %	HGB G/DL	RBC MILLS	WBC THS	DIFFERENTIAL					BLAST %	META %	BAND %	SEG %	LYMPH %	MONO %	EOSIN %	BASO %
1 0.0 MG/KG	50051	49.5	17.6	9.66	6.0	0	0	0	0	13	80	3	3	0	0	0	0	0
	50052	51.0	16.2	8.93	7.8	0	0	0	0	20	77	1	2	0	0	0	0	0
	50053	50.0	16.6	9.34	8.4	0	0	0	0	11	86	2	1	0	0	0	0	0
	50054	53.0	17.1	9.64	8.2	0	0	0	0	19	77	3	1	0	0	0	0	0
	50055	48.0	15.1	8.34	8.5	0	0	0	0	33	60	4	3	0	0	0	0	0
	MEAN	50.30	16.52	9.182	7.78													
	S.D.	1.86	0.93	0.556	1.03													
2 0.3 MG/KG	50151	55.0	17.8	9.30	9.6	0	0	0	0	30	66	2	2	0	0	0	0	0
	50152	49.5	16.4	9.26	7.4	0	0	0	0	17	78	4	1	0	0	0	0	0
	50153	49.0	16.4	8.85	4.4	0	0	0	0	39	57	3	1	0	0	0	0	0
	50154	48.5	16.2	8.36	7.3	0	0	0	0	21	75	3	0	0	0	0	0	0
	50155	50.0	16.2	9.63	5.5	0	0	0	0	22	76	2	0	0	0	0	0	0
	MEAN	50.40	16.60	9.080	6.84													
	S.D.	2.63	0.68	0.489	1.99													
3 1.0 MG/KG	50251	50.0	16.4	9.60	21.3	0	0	0	0	19	74	3	3	0	0	0	0	0
	50252	51.0	16.4	9.54	11.0	0	0	0	0	27	68	4	1	0	0	0	0	0
	50253	58.0	17.8	10.83	10.9	0	0	0	0	17	79	2	2	0	0	0	0	0
	50254	53.5	16.6	9.22	20.9	0	0	0	0	36	61	1	2	0	0	0	0	0
	50255	48.0	15.3	8.88	14.3	0	0	0	0	20	78	2	0	0	0	0	0	0
	MEAN	52.10	16.50	9.614	15.68 <sup>st</sup>													
	S.D.	3.85	0.89	0.738	5.14													
4 3.0 MG/KG	50351	47.5	16.2	9.36	11.4	0	0	0	0	21	76	3	0	0	0	0	0	0
	50352	51.5	15.8	9.18	13.2	0	0	0	0	29	69	2	0	0	0	0	0	0
	50353	50.5	15.8	8.88	9.8	0	0	0	0	23	77	0	0	0	0	0	0	0
	50354	52.0	16.0	8.45	5.6	0	0	0	0	19	78	2	1	0	0	0	0	0
	50355	49.5	17.1	8.63	11.3	0	0	0	0	16	82	2	0	0	0	0	0	0
	MEAN	50.30	16.18	8.900	10.26													
	S.D.	1.79	0.54	0.376	2.87													

APPENDIX 1 - CONTINUED  
INDIVIDUAL & MEAN HEMATOLOGY VALUES  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE

MALE - WEEK 52

GROUP NO AND DOSE LVL	ANIMAL NUMBER	HCT %	HGB G/DL	RBC MILLS	WBC THS	BLAST %	META %	BAND %	DIFFERENTIAL					BASO %
									SEG %	LYMPH %	MONO %	EOSIN %		
1 0.0 MG/KG	500001	48.0	15.5	9.29	11.2	0	0	0	18	82	0	0	0	
	500002	46.0	16.6	8.96	12.2	0	0	0	24	75	1	0	0	
	500003	48.0	15.1	9.94	12.9	0	0	1	27	72	0	0	0	
	500004	44.0	14.7	8.42	13.7	0	0	0	19	81	0	0	0	
	500005	41.0	15.1	8.74	13.6	0	0	0	28	71	1	0	0	
	MEAN	45.40	15.40	9.070	12.92									
	S.D.	2.97	0.73	0.581	1.33									
2 0.3 MG/KG	501001	50.0	16.8	8.85	13.3	0	0	0	35	64	0	1	0	
	501003	47.0	14.2	9.87	20.2	0	0	0	19	79	0	2	0	
	501004	47.0	15.9	9.73	14.3	0	0	1	26	73	0	0	0	
	501005	44.0	14.2	9.07	21.7	0	0	1	18	80	1	0	0	
	501006	43.0	14.2	7.87	27.8	0	0	1	34	65	0	0	0	
	MEAN	46.20	15.06	9.078	19.46									
	S.D.	2.77	1.22	0.801	5.91									
3 1.0 MG/KG	502002	45.0	14.7	9.18	19.1	0	0	0	14	86	0	0	0	
	502003	42.0	15.1	7.97	24.1	0	0	0	80	20	0	0	0	
	502004	44.0	15.5	9.26	17.6	0	0	0	50	49	1	0	0	
	502005	45.0	15.1	8.78	14.9	0	0	0	34	65	1	0	0	
	502006	46.0	15.1	9.23	15.3	0	0	0	23	77	0	0	0	
	MEAN	44.40	15.10	8.884	18.20									
	S.D.	1.52	0.28	0.547	3.72									
4 3.0 MG/KG	503002	47.0	13.1	8.31	18.7	0	0	0	19	81	0	0	0	
	503003	45.0	15.3	9.32	15.0	0	0	2	25	73	0	0	0	
	503004	47.0	11.6	7.88	33.5	0	0	0	57	42	1	0	0	
	503005	40.0	14.7	8.38	19.6	0	0	0	19	80	1	0	0	
	503007	47.0	14.7	9.97	13.1	0	0	0	37	62	1	0	0	
	MEAN	45.20	13.88	8.772	19.98									
	S.D.	3.03	1.51	0.851	8.01									

APPENDIX 1 - CONTINUED  
INDIVIDUAL & MEAN HEMATOLOGY VALUES  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE

FEMALE - WEEK 52

GROUP NO AND DOSE LVL	ANIMAL NUMBER	HCT %	HGB G/DL	RBC MILLS	WBC THS	DIFFERENTIAL					BASO %	
						BLAST %	MET %	BAND %	SEG %	LYMPH %		MONO %
1 0.0 MG/KG	50051	53.0	13.8	9.40	15.4	0	0	0	27	73	0	0
	50055	48.0	14.7	10.72	15.0	0	0	0	14	86	0	0
	50056	50.0	15.5	8.99	17.7	0	0	0	19	81	0	0
	50057	49.0	14.7	8.55	19.9	0	0	0	19	81	0	0
	50059	50.0	16.4	9.67	13.6	0	0	2	17	80	1	0
	MEAN	50.00	15.02	9.466	16.32							
	S.D.	1.87	0.98	0.819	2.49							
2 0.3 MG/KG	50151	52.0	17.1	10.12	15.8	0	0	0	25	75	0	0
	50152	46.0	14.4	9.29	14.6	0	0	0	15	85	0	0
	50153	46.0	14.2	8.67	2.6	0	0	1	38	61	0	0
	50154	46.0	15.1	8.74	5.0	0	0	0	20	80	0	0
	50155	45.0	14.2	10.13	17.0	0	0	0	30	70	0	0
	MEAN	47.00	15.00	9.390	11.00							
	S.D.	2.83	1.23	0.713	6.68							
3 1.0 MG/KG	50251	55.0	13.4	7.79	17.6	0	0	0	18	78	3	1
	50253	50.0	14.7	9.64	15.2	0	0	0	21	78	1	0
	50254	48.0	14.7	9.47	12.2	0	0	0	23	75	2	0
	50255	48.0	15.5	10.17	13.2	0	0	0	16	84	0	0
	50256	51.0	15.1	9.66	15.5	0	0	1	27	71	1	0
	MEAN	50.40	14.68	9.346	14.74							
	S.D.	2.88	0.79	0.908	2.11							
4 3.0 MG/KG	50351	48.0	16.8	9.39	9.9	0	0	0	8	92	0	0
	50352	51.0	15.5	9.32	16.3	0	0	0	14	86	0	0
	50353	47.0	15.5	9.11	11.6	0	0	0	8	92	0	0
	50354	50.0	15.5	8.99	16.6	0	0	1	24	75	0	0
	50355	49.0	14.8	9.02	14.6	0	0	0	13	86	1	0
	MEAN	49.00	15.62	9.166	13.80							
	S.D.	1.58	0.73	0.180	2.95							

APPENDIX 1 - CONTINUED  
INDIVIDUAL & MEAN HEMATOLOGY VALUES  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE  
MALE - WEEK 78

GROUP NO AND DOSE LVL	ANIMAL NUMBER	HCT %	HGB G/DL	RBC MILLS	WBC THS	BLAST %	META %	BAND %	DIFFERENTIAL					BASO %
									SEG %	LYMPH %	MONO %	EUSIN %		
1 0.0 MG/KG	50002	40.0	12.8	10.66	18.8	0	0	4	54	40	2	0	0	
	50003	48.0	15.2	10.96	13.1	0	0	1	39	59	0	1	0	
	50004	43.5	14.4	8.81	16.5	0	0	0	46	53	0	1	0	
	50005	44.0	15.0	9.41	9.8	0	0	3	36	61	0	0	0	
	50006	44.0	15.4	10.66	7.6	0	0	1	26	71	2	0	0	
	MEAN S.D.	43.90 2.84	14.56 1.05	10.100 0.936	13.16 4.61									
2 0.3 MG/KG	50101	44.5	14.6	9.00	9.7	0	0	0	33	67	0	0	0	
	50104	49.0	15.7	10.59	6.6	0	0	0	25	73	1	1	0	
	50105	42.0	12.2	8.44	21.2	0	0	1	20	79	0	0	0	
	50106	41.0	12.8	8.53	23.3	0	0	2	52	46	0	0	0	
	50107	41.5	12.4	8.66	9.8	0	0	0	49	51	0	0	0	
	MEAN S.D.	43.60 3.31	13.54 1.54	9.044 0.890	14.12 7.57								46	
3 1.0 MG/KG	50203	49.5	16.4	10.02	9.9	0	0	0	63	36	1	0	0	
	50206	43.0	12.0	8.82	9.1	0	0	2	72	24	2	0	0	
	50207	40.0	11.8	8.23	19.9	0	0	3	34	61	0	2	0	
	50208	49.0	14.4	9.04	17.3	0	0	1	27	72	0	0	0	
	50209	44.0	12.2	8.65	26.6	0	0	3	40	55	1	1	0	
	MEAN S.D.	45.10 4.07	13.36 2.00	8.952 0.667	16.56 7.29									
4 3.0 MG/KG	50302	36.5	9.3	6.41	40.7	0	0	0	75	25	0	0	0	
	50303	43.0	13.7	8.15	14.2	0	0	0	44	54	1	1	0	
	50307 <sup>a</sup>	41.0	11.3	8.19	55.5	0	0	5	59	36	0	0	0	
	50308 <sup>a</sup>	28.5	6.6	4.22	31.1	0	0	0	56	44	0	0	0	
	50311	48.0	14.6	9.47	15.2	0	0	1	19	77	2	1	0	
	MEAN S.D.	39.40 7.36	11.10 3.26	7.288 <sup>S-</sup> 2.031	31.34 17.50									

<sup>a</sup> Slight anisocytosis and moderate polychromatophilia.



APPENDIX 1 - CONTINUED  
INDIVIDUAL & MEAN HEMATOLOGY VALUES  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE  
FEMALE - WEEK 78

GROUP NO AND DOSE LVL	ANIMAL NUMBER	HCT %	HGB G/DL	RBC MILLS	WBC THS	DIFFERENTIAL									
						BLAST %	MF1A %	BAND %	SEG %	LYMPH %	MJVO %	EOSIN %	BASO %		
1 0.0 MG/KG	50051	41.5	14.1	7.72	16.5	0	0	1	37	59	2	1	0		
	50055	45.5	13.7	10.02	10.5	0	0	3	48	44	0	5	0		
	50056	41.0	11.5	8.11	27.6	0	0	2	45	51	1	1	0		
	50059	49.0	14.6	9.70	9.4	0	0	2	11	87	0	0	0		
	50061	43.5	13.0	8.70	17.5	0	0	1	29	70	0	0	0		
	MEAN	44.10	13.38	8.850	16.30										
	S.D.	3.27	1.20	0.992	7.25										
2 0.3 MG/KG	50151	48.0	15.2	10.43	18.7	0	0	2	28	70	0	0	0		
	50152	41.0	11.3	7.58	10.4	0	0	0	28	71	0	1	0		
	50153	45.0	13.2	9.18	19.6	0	0	2	43	53	1	1	0		
	50154	39.0	14.4	8.59	7.6	0	0	0	31	68	0	1	0		
	50155	40.0	15.0	9.41	9.8	0	0	0	24	76	0	0	0		
	MEAN	42.60	13.82	9.038	13.22										
	S.D.	3.78	1.61	1.052	5.52										
3 1.0 MG/KG	50251	43.5	12.6	8.13	8.4	0	0	2	37	57	3	1	0		
	50253	52.5	14.1	9.76	13.6	0	0	0	12	88	0	0	0		
	50255	50.0	14.4	9.70	9.7	0	0	1	21	78	0	0	0		
	50256 <sup>a</sup>	44.0	12.6	8.96	12.3	0	0	0	41	59	0	0	0		
	50257 <sup>a</sup>	34.5	9.2	6.64	11.6	0	0	1	60	39	0	0	0		
	MEAN	44.90	12.58	8.638	11.12										
	S.D.	6.98	2.06	1.298	2.07										
4 3.0 MG/KG	50351	46.5	13.5	8.91	10.3	0	0	2	22	74	2	0	0		
	50352	50.0	15.2	9.66	10.9	0	0	0	20	79	1	0	0		
	50353	42.0	12.2	8.51	20.2	0	0	0	36	62	1	1	0		
	50354	40.5	11.8	8.00	10.8	0	0	0	28	71	0	1	0		
	50355	46.0	13.5	9.45	19.0	0	0	3	22	74	1	0	0		
	MEAN	45.00	13.24	8.906	14.24										
	S.D.	3.79	1.34	0.679	4.92										

<sup>a</sup> Slight anisocytosis.

APPENDIX 2  
INDIVIDUAL & MEAN CLINICAL CHEMISTRY VALUES  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE

MALE - WEEK 78

GROUP NO AND DOSE LVL	ANIMAL NUMBER	SGPT IU/L	SGPT IU/L	ALK PHOS IU/L	ALB MG/DL	CHE RBC DELTA PH/MIN	CHE PLASMA DELTA PH/MIN	CHE BRAIN DELTA PH/MIN	FASTING GLUCOSE MG/DL	TOTAL PROTEIN G/DL
1 0.0 MG/KG	50003	60	9	31	61.3				93	4.2
	50005	51	10	20	45.5				91	4.3
	50006 <sup>a</sup>	57	10	29	63.2				101	4.6
	50009	52	9	22	81.3				74	3.3
	50011	*QNS	10	26	117.9				QNS	3.4
	50014	178	26	29	143.2				109	4.1
	50015	*QNS	6	*QNS	QNS				QNS	3.8
	50018	*QNS	10	32	69.2				QNS	4.1
	50041					0.75	2.21	2.54		
	50042					0.50	2.29	3.53		
	50043					0.54	2.35	3.23		
	50045					0.51	2.32	3.37		
2 0.3 MG/KG	50048					0.56	2.38	3.04		
	MEAN	79.6	11.2	27.0	68.80	0.573	2.311	3.141	93.6	4.10
	S.D.	55.1	6.1	4.5	25.34	0.103	0.065	0.382	13.1	0.40
	50104 <sup>b</sup>	44	16	46	52.4				109	4.6
	50105	53	10	23	71.0				93	4.8
	50107	*QNS	9	*QNS	QNS				QNS	4.8
	50108	79	10	43	61.7				136	4.1
	50109	54	9	21	79.8				80	4.4
	50110	93	9	26	66.5				103	3.9
	50116	92	7	26	98.4				QNS	5.3
	50142					0.58	2.27	3.83		
	50143					0.50	2.31	3.37		
	50144					0.44	2.39	3.63		
	50148					0.46	2.22	2.74		
	50149					0.45	2.33	2.99		
	MEAN	69.3	10.8	30.8	71.63	0.486	2.305	3.311	104.2	4.56
	S.D.	21.3	2.8	10.8	15.99	0.059	0.065	0.446	20.9	0.47

\* QNS - Quantity not sufficient to perform analysis.

<sup>a</sup> Slight hemolysis.

<sup>b</sup> Very slight hemolysis.

APPENDIX 2 - CONTINUED  
INDIVIDUAL & MEAN CLINICAL CHEMISTRY VALUES  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE

MALE - WEEK 78

GROUP NO AND DOSE LVL	ANIMAL NUMBER	SGPT IU/L	SGPT IU/L	ALK PHOS IU/L	BUN MG/DL	CHF RBC DELTA PH/MIN	CHF PLASMA DELTA PH/MIN	CHF BRAIN DELTA PH/MIN	FASTING GLUCOSE MG/DL	TOTAL PROTEIN G/DL
1.0 MG/KG 3	50207	*QNS	77	23	108.8				QNS	4.5
	50208	116	16	61	77.8				98	3.8
	50210	53	12	23	27.4				QNS	4.0
	50212	59	15	97	35.6				80	5.0
	50214									
	50215	88	10	111	85.4				QNS	4.1
	50222	55	15	25	47.8	0.69	2.33	3.02	47	4.5
	50223	69	8	47	43.2	0.50	2.19	3.18	60	4.4
	50240					0.39	2.25	3.58		
	50241					0.43	2.34	2.51		
	50247					0.39	2.38	3.12		
	50248									
3.0 MG/KG 4	MEAN	73.3	21.9	55.3	60.86	0.480	2.299	3.082	71.2	4.33
	S.D.	24.5	24.5	36.4	30.08	0.128	0.077	0.386	22.4	0.40
	50303	*QNS	35	97	34.3				QNS	5.3
	50307	88	16	19	37.9				QNS	5.7
	50308	42	16	9	47.0				29	4.0
	50312	*QNS	10	*QNS	*QNS				QNS	4.1
	50315	*QNS	25	*QNS	*QNS				QNS	4.0
	50316	120	13	36	60.7				94	4.4
	50317	61	10	31	48.3				115	4.5
	50319	143	20	18	42.1				124	4.3
	50343					0.53	2.25	3.00		
	50345					0.52	2.26	2.69		
	50347					0.49	2.15	3.13		
	50348					0.56	2.30	2.82		
	50350					0.48	2.31	3.02		
	MEAN	90.8	18.1	35.0	45.05	0.514	2.255	2.935	90.5	4.54
	S.D.	41.4	8.5	31.9	9.32	0.032	0.062	0.174	42.9	0.63

\*QNS - Quantity not sufficient to perform analysis.

APPENDIX 2 - CONTINUED  
INDIVIDUAL & MEAN CLINICAL CHEMISTRY VALUES  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE

FEMALE - WEEK 78

GROUP NO AND DOSE LVL	ANIMAL NUMBER	SGOT IU/L	SGPT IU/L	ALK PHOS IU/L	BUN MG/DL	CHE RBC DELTA PH/MIN	CHE PLASMA DELTA PH/MIN	CHE BRAIN DELTA PH/MIN	FASTING GLUCOSE MG/DL	TOTAL PROTEIN G/DL
1 0.0 MG/KG	50051	328+	20	33	61.2				QNS	4.2
	50055	152	10	42	69.9				QNS	4.7
	50059	152	10	25	38.4				91	3.8
	50061	108	11	70	78.1				QNS	4.6
	50063 <sup>a</sup>	74	10	65	64.5				34	4.2
	50064 <sup>a</sup>	79	11	34	76.1				40	4.9
	50065					0.51	2.32	2.82		
	50096					0.63	2.33	2.65		
	50098					0.78	2.36	2.20		
	50099					0.64	2.30	3.32		
2 0.3 MG/KG	50100					0.58	2.29	3.45		
	MEAN	113.0	12.0	44.83	64.70	0.631	2.320	2.888	55.0	4.40
	S.D.	37.9	3.9	18.43	14.43	0.102	0.025	0.507	31.3	0.40
	50152	330	32	31.	111.4				QNS	5.9
	50154	*QNS	47	56	87.4				QNS	3.7
	50155 <sup>a</sup>	133	21	125	54.9				QNS	5.3
	50157 <sup>a</sup>	60	12	101	44.2				84	4.9
	50158 <sup>a</sup>	86	11	60	35.2				QNS	4.2
	50159 <sup>b</sup>	70	12	110	38.2				60	4.7
	50160 <sup>b</sup>	56	11	61	47.4				100	4.7
	50194					0.54	2.28	3.0		
	50195					0.88	2.26	3.3		
	50197					0.91	2.29	2.7		
	50198					0.63	2.35	3.0		
	50199					0.70	2.33	3.4		
	MEAN	123.3	16.5	77.7	59.81	0.733	2.303	3.122	81.3	4.77
	S.D.	105.6	8.5	34.3	28.63	0.161	0.035	0.269	20.1	0.71

\*QNS - Quantity not sufficient to perform determination.

<sup>a</sup> Very slight hemolysis.

<sup>b</sup> Moderate hemolysis.

APPENDIX 2 - CONTINUED  
INDIVIDUAL & MEAN CLINICAL CHEMISTRY VALUES  
78-WEEK TOXICITY AND CARCINOGENICITY STUDY OF DBCP IN MICE

FEMALE - WEEK 78

GROUP NO AND DOSE LVL	ANIMAL NUMBER	SGPT IU/L	SGPT IU/L	ALK IU/L	BUN MG/DL	CHE RBC DELTA PH/MIN	CHE PLASMA DELTA PH/MIN	CHE BRAIN DELTA PH/MIN	FASTING GLUCOSE MG/DL	TOTAL PROTEIN G/DL
3 0.0 MG/KG	50251	255	13	83	93.8				QNS	4.2
	50255	275	34	47	38.6				109	4.9
	50256	55	9	33	48.3				100	5.0
	50257	147	10	64	81.4				QNS	5.0
	50258 <sup>a</sup>	159	10	35	45.9				61	4.8
	50259	131	12	32	115.9				83	4.2
	50261	61	12	45	59.0				100	4.2
	50294					0.87	2.33	2.79		
	50296					0.69	2.39	2.52		
	50297					0.60	2.33	3.02		
4 3.0 MG/KG	50298					0.52	2.35	2.84		
	50300					0.48	2.35	2.78		
	MFAN	140.4	14.3	48.43	68.99	0.631	2.351	2.790	90.6	4.61
	S.D.	92.7	8.8	18.88	28.74	0.156	0.025	0.178	19.0	0.39
	50351	114	13	53	40.3				111	4.7
	50352	124	21	86	38.5				110	4.5
	50354	198	13	38	54.7				105	5.1
	50355	*QNS	14	*QNS	*QNS				QNS	4.2
	50356	116	22	74	96.6				78	3.4
	50357	88	32	78	42.8				52	3.8
	50390					0.59	2.48	1.96		
	50391					0.65	2.28	2.65		
	50394					0.97	2.38	2.94		
	50395					0.62	2.33	2.67		
	50396					0.61	2.40	2.36		
	MFAN	128.0	19.2	65.8	54.58	0.685	2.375	2.517	91.2	4.28
	S.D.	41.4	7.5	19.7	24.33	0.159	0.074	0.371	25.7	0.62

\* QNS -Quantity not sufficient to perform determination.

<sup>a</sup> Slight hemolysis.

Appendix 3  
Analysis of DBCP Content in Diet Mixtures  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice

Group/ Sex	Target Conc. (ppm)	Week 8				72 Hrs	% DBCP <sup>a</sup> Remaining in Diet at 72 Hrs
		0 Hr	Concentration Found (ppm)		48 Hrs		
			24 Hrs	48 Hrs			
2-Males	3.60	4.68	2.57	1.43	0.67	14	
2-Females	3.10	2.01	1.58	0.89	0.23	11	
3-Males	12.28	13.99	13.18	7.50	3.58	26	
3-Females	11.47	11.04	9.39	5.51	3.47	31	
4-Males	36.05	34.51	30.79	14.10	9.36	27	
4-Females	30.58	36.38	27.94	19.19	7.30	30	
Week 13							
2-Males	4.70	3.13	1.83	1.37	1.04	33.23	
2-Females	4.12	2.80	1.57	1.13	0.64	22.86	
3-Males	16.27	6.30	4.93	3.77	2.72	43.17	
3-Females	14.11	6.30	4.63	4.29	2.97	47.14	
4-Males	49.00	20.29	11.86	13.51	11.60	57.17	
4-Females	40.77	27.27	18.75	10.91	8.55	31.35	
Week 26							
2-Males	3.78	2.5	2.3	1.4	1.1	44	
2-Females	3.78	2.8	1.8	1.3	1.3	46	
3-Males	12.74	7.7	5.9	5.0	2.7	35	
3-Females	12.74	8.6	6.4	7.7	4.1	48	
4-Males	39.34	35.7	27.0	23.5	13.5	38	
4-Females	37.10	28.5	21.9	17.1	9.8	37	

<sup>a</sup> Percent DBCP remaining in feed is [concentration of DBCP at 72 Hours ÷ concentration of DBCP at 0 Hrs] x 100.

Appendix 3 - Continued  
Analysis of DBCP Content in Diet Mixtures  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice

Week 42

Group/ Sex	Target Conc. (ppm)	0 Hr	Concentration Found (ppm)		72 Hrs	% DBCP <sup>a</sup> Remaining in Diet at 72 Hrs
			24 Hrs	48 Hrs		
2-Males	3.9 <sup>b</sup>	2.5	1.6	1.1	0.81	32
2-Females	3.2 <sup>b</sup>	1.5	1.3	0.68	0.65	43
3-Males	13.5 <sup>b</sup>	9.7	6.3	3.7	2.5	26
3-Females	9.8 <sup>b</sup>	6.7	4.0	2.5	2.1	31
4-Males	39.9 <sup>b</sup>	36.4	26.1	16.3	13.6	37
4-Females	35.1 <sup>b</sup>	11.2	9.2	8.0	6.8	61

Week 50

2-Males	4.9 <sup>b</sup>	3.2	2.6	1.8	1.1	34
2-Females	4.4 <sup>b</sup>	3.4	2.4	1.8	1.3	38
3-Males	16.2 <sup>b</sup>	9.5	7.1	4.9	4.7	49
3-Females	12.3 <sup>b</sup>	5.1	4.4	3.3	2.3	45
4-Males	46.4 <sup>b</sup>	44.1	21.2	20.0	17.2	39
4-Females	34.7 <sup>b</sup>	21.8	14.9	13.7	13.7	63

Week 65

2-Males	4.76 <sup>b</sup>	6	4	3	2	33
2-Females	4.62 <sup>b</sup>	5	3	4	3	60
3-Males	16.24 <sup>b</sup>	19	15	11	8	42
3-Females	13.72 <sup>b</sup>	19	14	10	9	47
4-Males	50.96 <sup>b</sup>	61	52	30	29	47
4-Females	41.58 <sup>b</sup>	44	39	31	18	41

<sup>a</sup> Percent DBCP remaining in feed is [concentration of DBCP at 72 Hours ÷ concentration of DBCP at 0 Hrs] x 100.

<sup>b</sup> Target concentrations of DBCP based upon intended levels specified by design and incorrectly calculated food consumption values which were one-half of the mathematically correct values.

Appendix 3 - Continued  
Analysis of DBCP Content in Diet Mixtures  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice

Group/ Sex	Target Conc. (ppm)	Week 77 <sup>c</sup>				% DBCp <sup>a</sup> Remaining in Diet at 72 Hrs
		0 Hr	Concentration Found (ppm)		72 Hrs	
			24 Hrs	48 Hrs		
2-Males	4.76 <sup>b</sup>	3.75	-	-	-	
2-Females	4.90 <sup>b</sup>	3.75	-	-	-	
3-Males	17.92 <sup>b</sup>	19.7	-	-	-	
3-Females	16.10 <sup>b</sup>	14.5	-	-	-	
4-Males	57.68 <sup>b</sup>	70.0	-	-	-	
4-Females	42.56 <sup>b</sup>	54.0	-	-	-	

<sup>a</sup> Percent DBCP remaining in feed is [concentration of DBCP at 72 Hours ÷ concentration of DBCP at 0 Hrs] x 100.

<sup>b</sup> Target concentrations of DBCP based upon intended levels specified by design and incorrectly calculated food consumption values which were one-half of the mathematically correct values.

<sup>c</sup> Samples of diet at 24, 48, and 72 hours were not taken.



KEY TO APPENDIX 4

Type of Finding

0 = Tissue Absent

X = Tissue Examined and Not Remarkable

A = Autolysis

P = Finding Present

Grading or Degree of Finding

1 = Minimal

2 = Slight

3 = Moderate

4 = Moderately Severe

5 = Severe

Time of Sacrifice

a = Terminally Sacrificed

b = Sacrificed in Extremis

c = Found Dead

d = Unknown

## Appendix 4

### Individual Histopathology Findings

## 78-Week Toxicity and Carcinogenicity Study of DBCP in Mice

**Males**

	Group 1 - 0.0 mg/kg/day																	
	5b	5a	5a	5c	5a	5c	5a	5b	5a	5c	5a	5c	5a	5b	5a	5c	5a	5c
Animal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Number:	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8

## ORGAN AND DESCRIPTION

## HEART

Atrial Thrombosis  
Diffuse Amyloidosis

## LUNG

## Focal Pneumonitis

## SPLEEN

Pancreatic Tissue Attached to Splenic Capsule

## Amyloidosis

## LIVER

Hepatocellular Adenoma  
Microgranulomas  
Areas of Altered Cells  
Focal Hepatic Necrosis  
Amyloidosis

Perivascular Lymphoid Foci

## Congestion

Centrilobular Hepatocytic Swelling

### Nonsuppurative Pericholangitis

## KIDNEY

Perivascular Lymphoid Foci

Amvloidosis

## Interstitial Nephritis

**Congestion**

## Congestion Distension of Renal Pelvis

## DISCUSSION OF Hydronephrosis

## Myeloneuropilosis Cortical Cysts

Appendix 4 - Continued  
Individual Histopathology Findings  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Males

	Group 1 - 0.0 mg/kg/day																							
	5b	5a	5a	5c	5a	5a	5c	5c	5a	5a	5c	5c	5a	5a	5c	5b	5a	5b	5b	5a	5a	5a	5c	5a
Animal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Number:	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4

ORGAN AND DESCRIPTION

STOMACH	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Amyloidosis																								
TESTES	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Mineralized Seminiferous Tubules																								
Unilateral Hypospermatogenesis																								
Bilateral Hypospermatogenesis																								
Amyloidosis																								
MESENTERIC LYMPH NODES																								
Sinus Histiocytosis																								
AXILLARY LYMPH NODES																								
LYMPH NODES IN ABDOMINAL AREA																								
Sinus Histiocytosis																								
ESOPHAGUS																								
Inflammatory Cell Infiltration																								
(Adjacent Tissue)																								
Necrosis (Adjacent Tissue)																								

Appendix 4 - Continued  
Individual Histopathology Findings  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Males

ORGAN AND DESCRIPTION	Group 1 - 0.0 mg/kg/day																							
	5c	5a	5b	5a	5a	5a	5c	5c	5a	5a	5a	5c	5c	5a	5a	5a	5a	5c	5c	5a	5c	5c	5c	5c
HEART																								
Granulomatous Epicarditis																								
LUNG																								
Congestion																								
Bacterial Pleuritis																								
LIVER																								
Microgranulomas																								
Focal Hepatic Necrosis																								
Amyloidosis																								
Perivascular Lymphoid Foci																								
Congestion																								
Centrilobular Hepatocytic Degeneration																								
Nonsuppurative Pericholangitis																								
Focal Nonsuppurative Hepatitis																								
KIDNEY																								
Perivascular Lymphoid Foci																								
Amyloidosis																								
Interstitial Nephritis																								
Congestion																								
Focal Mineralization in Cortex																								
Nonsuppurative Pyelitis																								
STOMACH																								
Amyloidosis																								
Focal Ulceration																								

Appendix 4 - Continued  
 Individual Histopathology Findings  
 78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
 Males

	Group 1 - 0.0 mg/kg/day																	
	5c	5a	5b	5a	5a	5c	5c	5a	5a	5c	5a	5a	5a	5a	5c	5a	5c	5c
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Animal	2	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Number:	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3

ORGAN AND DESCRIPTION

TESTES	X																	
Mineralized Seminiferous Tubules																		
Unilateral Hypospermatogenesis																		
Bilateral Hypospermatogenesis																		
Amyloidosis																		
Nonsuppurative Epididymitis																		
Bilateral Aspermatogenesis																		
UNUSUAL LESIONS																		
Galactoceles																		

Appendix 4 - Continued  
Individual Histopathology Findings  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Females

		Group 1 - 0.0 mg/kg/day																							
		5a	5c	5c	5c	5a	5a	5c	5b	5a	5c	5a	5a	5a	5b	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Animal	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Number:	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5

ORGAN AND DESCRIPTION

SPLEEN																								
Hemangiosarcoma		P																						
Increased Extramedullary Hematopoiesis		P																						
LIVER																								
Microgranulomas		X																						
Amyloidosis		P																						
Perivascular Lymphoid Foci		P																						
Congestion		P																						
Centrilobular Hepatocytic Degeneration		P																						
Nonsuppurative Pericholangitis		P																						
Cholangiectasis		P																						
Thrombosed Vessel		P																						
KIDNEY																								
Malig. Lymphoma, Histiocytic Type		P																						
Perivascular Lymphoid Foci		P																						
Amyloidosis		P																						
Interstitial Nephritis		P																						
Congestion		P																						
Hydronephrosis		P																						
Nonsuppurative Pyelitis		P																						
STOMACH																								
Amyloidosis		X																						
Focal Ulceration		P																						
Hemorrhage		P																						
PANCREAS		X																						

Appendix 4 - Continued  
 Individual Histopathology Findings  
 78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
 Females

		Group 1 - 0.0 mg/kg/day																														
		5a	5c	5c	5c	5a	5a	5a	5b	5a	5c	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5c	5a	5a	5a	5a	5a	5a	5a		
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Animal	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5		
Number:	1	2	3	4	5	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5						

ORGAN AND DESCRIPTION

OVARY

Hematocyst

UTERUS

Cystic Endometrial Hyperplasia

Hematocyst

MESENTERIC LYMPH NODES

Malign. Lymphoma, Histiocytic Type

Lymphoreticular Cell Proliferation

Leukemoid Response

P

P

P

P

P

P

Appendix 4 - Continued  
Individual Histopathology Findings  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Females

	Group 1 - 0.0 mg/kg/day																	
	5a	5b	5a	5a	5c	5b	5a	5a	5a	5a	5a	5a	5b	5c	5c	5a	5b	5a
Animal	7	7	7	7	8	8	8	8	8	8	8	8	9	9	9	9	9	9
Number:	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3

ORGAN AND DESCRIPTION

LUNG																		
Alveolar/Bronchiolar Hyperplasia																		
SPLEEN																		
Amyloidosis																		
Increased Extramedullary Hematopoiesis																		
Sinusoidal Ectasia																		
LIVER																		
Microgranulomas																		
Focal Hepatic Necrosis																		
Amyloidosis																		
Congestion																		
Focal Leukemoid Response																		
Cholangiectasis																		
KIDNEY																		
Perivascular Lymphoid Foci																		
Amyloidosis																		
Interstitial Nephritis																		
Congestion																		
Hydronephrosis																		
Renal Tubule Cell Hyperplasia																		
Cholemic Nephrosis																		
STOMACH																		
Amyloidosis																		



Appendix 4 - Continued  
 Individual Histopathology Findings  
 78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
 Females

		Group 1 - 0.0 mg/kg/day																								
		5a	5b	5a	5a	5c	5a	5a	5a	5a	5a	5a	5b	5c	5c	5c	5a	5b	5a	5c	5a	5a	5a			
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0			
		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1			
Animal		7	7	7	7	8	8	8	8	8	8	8	8	9	9	9	9	9	9	9	9	9	0			
Number:		6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0

ORGAN AND DESCRIPTION

OVARY

Hematocyst

UTERUS

Cystic Endometrial Hyperplasia

Hematocyst

MESENTERIC LYMPH NODES

Congestion

P

P

P

P

P

P

Appendix 4 - Continued  
Individual Histopathology Findings  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Males

	Group 4 - 3.0 mg/kg/day																									
	5c	5c	5a	5b	5b	5b	5a	5a	5c	5b	5a	5a	5a	5c	5a	5b	5c	5a	5c	5b	5a	5c	5a	5b	5c	
Animal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Number:	1	2	3	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5

ORGAN AND DESCRIPTION

LUNG																									
Malig. Lymphoma, Stem Cell Type																									
Spleen																									
Malig. Lymphoma, Stem Cell Type																									
LIVER																									
Malig. Lymphoma, Stem Cell Type																									
Metastatic Squamous Cell Carcinoma																									
Microgranulomas																									
Focal Hepatic Necrosis																									
Amyloidosis																									
Congestion																									
Nonsuppurative Pericholangitis																									
KIDNEY																									
Malig. Lymphoma, Stem Cell Type																									
Metastatic Squamous Cell Carcinoma																									
Pyelonephritis																									
Perivascular Lymphoid Foci																									
Amyloidosis																									
Interstitial Nephritis																									
Congestion																									
Cortical Cysts																									
Focal Mineralization in Cortex																									
Megalocytic Cells																									

- 65 -

[illegible]

Appendix 4 - Continued  
Individual Histopathology Findings  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Males

	Group 4 - 3.0 mg/kg/day																							
	5a	5b	5a	5c	5a	5c	5a	5c	5a	5c	5a	5c	5a	5c	5a	5c	5a	5c	5a	5c	5a	5c	5a	5b
Animal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Number:	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	2	2	2	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9

ORGAN AND DESCRIPTION

ADRENAL																									
Metastatic Squamous Cell Carcinoma	P																								
SPLEEN																									
Metastatic Squamous Cell Carcinoma	P																								
Increased Extramedullary Hematopoiesis																									
LIVER																									
Hepatocellular Adenoma																									
Metastatic Squamous Cell Carcinoma	P	P																							
Microgranulomas	P	P	P																						
Focal Hepatic Necrosis																									
Amyloidosis																									
Perivascular Lymphoid Foci																									
Congestion																									
Hyperplastic Nodule																									
KIDNEY																									
Renal Tubule Carcinoma																									
Pyelonephritis																									
Perivascular Lymphoid Foci																									
Amyloidosis																									
Interstitial Nephritis																									
Congestion																									
Hydronephrosis																									
Cortical Cysts																									
Megalocytic Cells																									

## Group 4 - 3.0 mg/kg/day

## ORGAN AND DESCRIPTION

## ABDOMINAL MUSCLE AND DIAPHRAGM

## Squamous Cell Carcinoma, Metastatic

TESTES  
Mineralized Senuiferous Tubules  
Unilateral Hypospermatogenesis  
Bilateral Hypospermatogenesis

PROSTATE  
Suppurative Necrotizing Prostatitis

## MESENTERIC LYMPH NODES

**Amyloidosis  
Congestion**

Appendix 4 - Continued  
Individual Histopathology Findings  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Females

	Group 4 - 3.0 mg/kg/day																							
	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a
Animal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Number:	1	2	3	4	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5

ADRENAL																								
Pheochromocytoma																								
LUNG																								
Alveolar/Bronchiolar Adenoma																								
SPLEEN																								
Increased Extramedullary Hematopoiesis																								
LIVER																								
Hepatocellular Carcinoma																								
Metastatic Squamous Cell Carcinoma																								
Microgranulomas																								
Amyloidosis																								
Perivascular Lymphoid Foci																								
Congestion																								
KIDNEY																								
Perivascular Lymphoid Foci																								
Amyloidosis																								
Interstitial nephritis																								
Congestion																								
Cortical Cysts																								
Pigment																								
Hydronephrosis																								
STOMACH																								
Squamous Cell Carcinoma																								
Squamous Cell Papilloma																								
Amyloidosis																								
Focal Ulceration																								
Increased Basal Cell Activity																								
Acanthosis																								
Hyperkeratosis																								

Appendix 4 - Continued  
 Individual Histopathology Findings  
 78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
 Females

	Group 4 - 3.0 mg/kg/day																	
	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a	5a
Animal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Number:	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8

ORGAN AND DESCRIPTION

PANCREAS

SMALL INTESTINE

Amyloidosis

UTERUS

Fibrosarcoma

Endometrial Stromal Polyp

Cystic Endometrial Hyperplasia

MESENTERIC LYMPH NODES

Suppurative Necrotizing Lymphadenitis

AXILIARY LYMPH NODES

Lymphoreticular Cell Proliferation

SUBLUMBAR LYMPH NODES

Lymphoreticular Cell Proliferation

X

P

P

P

P

69

P

Appendix 4 - Continued  
Individual Histopathology Findings  
78-Week Toxicity and Carcinogenicity Study of DBCP in Males  
Females

	Group 4 - 3.0 mg/kg/day																	
	5a	5a	5a	5a	5a	5c	5c	5c	5b	5a	5a	5a	5a	5a	5a	5a	5c	5b
Animal	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Number:	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	4
	7	7	7	7	8	8	8	8	8	8	8	9	9	9	9	9	9	0
	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	3

ORGAN AND DESCRIPTION

PITUITARY

Adenoma

P

LUNG

Alveolar/Bronchiolar Adenoma  
Alveolar/Bronchiolar Carcinoma  
Focal Pneumonitis

P

P

SPLEEN

Increased Extramedullary Hematopoiesis

P

P

LIVER

Hepatocellular Adenoma  
Microgranulomas  
Focal Hepatic Necrosis  
Amyloidosis  
Perivascular Lymphoid Foci  
Congestion  
Diffuse Hepatitis  
Cholangiectasis

P

P

P

P

P

P

P

P

P

P

P

KIDNEY

Perivascular Lymphoid Foci  
Amyloidosis  
Interstitial Nephritis  
Congestion  
Hydronephrosis  
Cortical Cysts

X

X

X

X

X

X

X

X

X

X

X

X

X

X

X

X

X

X

X

X





Appendix 5  
References for Clinical Laboratory Studies  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Hematology

Hematocrit (HCT)

Strumia, et. al., Am. J. Clin. Pathol., XXIV 91954, p. 1016.

Hemoglobin (HGB)

Hycel Kit, Literature No. 5522S, Hycel Inc., Houston, Texas.

Erythrocyte Count (RBC)

Method outlined for Coulter Counter Model F, Coulter Electronics, Hialeah, Florida.

Leukocyte Count (WBC)

Method outlined for Coulter Counter Model F, Coulter Electronics, Hialeah, Florida.

Leukocyte Differential (Differential)

Rich, Lon J., Morphology of Canine and Feline Blood Cells, Ralston Purina Co., St. Louis, Mo., 1974. Diggs, L. W., Sturm, D., and Bell, A., The Morphology of Human Blood Cells., U. of Tenn., Col. of Med., Memphis, Tennessee.

Mean Corpuscular Volume (MCV)

$(\text{Hematocrit} \times \text{ten}) \div \text{Erythrocyte Count (Calculated)}.$

Mean Corpuscular Hemoglobin (MCH)

$(\text{Hemoglobin} \times \text{ten}) \div \text{Erythrocyte Count (Calculated)}.$

Mean Corpuscular Hemoglobin Concentration (MCHC)

$(\text{Hemoglobin} \times \text{one hundred}) \div \text{Hematocrit (Calculated)}.$

Erythrocyte Morphology

Rich, Lon J., Morphology of Canine and Feline Blood Cells, Ralston Purina Co., St. Louis, Mo., 1974 Diggs, L. W., Sturm, D., and Bell, A., The Morphology of Human Blood Cells., U. of Tenn., Col. of Med., Memphis, Tennessee.

Appendix 5 - Continued  
References for Clinical Laboratory Studies  
78-Week Toxicity and Carcinogenicity Study of DBCP in Mice  
Blood Chemistry

Red Cell Cholinesterase (RBC CHE), Plasma Cholinesterase (Plasma CHE),  
and Brain Cholinesterase (Brain CHE)

Delta pH Method - Michel, Harry O., An Electrometric Method for  
the Determination of Red Blood Cell and Plasma Cholinesterase  
Activity, The Journal of Laboratory and Clinical Medicine, XXXIV,  
No. 11, Nov. 1949, pp. 1564-1568.

The following parameters were performed by the reference given below:

Centrifichem Method - Union Carbide Corp., Clinical Diagnostics,  
401 Theodore Fremd Ave., Rye, New York 10580.

Serum Glutamic Oxaloacetic Transaminase (SGOT)  
Serum Glutamic Pyruvic Transaminase (SGPT)  
Alkaline Phosphatase (ALK PHOS)  
Blood Urea Nitrogen (BUN)  
Fasting Glucose  
Total Protein



- 74 -

APPENDIX 6

DETAILED EXPLANATION OF DOSAGE MISCALCULATION

Documented by

Office of Quality Assurance  
Hazleton Laboratories America, Inc.



# HAZLETON

LABORATORIES AMERICA, INC.

TO: File 174-125  
Howard  
Piccirillo  
Fezio

CC: Reno  
Weatherholtz  
Dagnall

DATE: 5/5/78

SUBJECT: Miscalculation of Dosage

FROM: OQA  
S. Hinkle *sh*

BLDG.

ROOM:

The data for this study indicate that beginning on 1/10/77 (week 28) and continuing through 12/23/77 (week 77) all test animals were dosed incorrectly based on inaccurate calculations of feed consumption. For weeks 1-27 (animals were group housed) and weeks 78-80 (animals were individually housed) the calculations appear to be correct. During weeks 28-77, the animals received approximately twice the desired amount of compound based on "feed consumption" data.

The error occurred when double the actual number of animals per group was used to find the mean weekly food consumption. For example in week 28 the total feed remaining for Group 2 $\sigma^7$  in 86 feeders (43 animals fed twice) was 12784.3g. This amount was subtracted from 15050g, the total amount fed that week (86 feeders x 175g each) leaving a remainder of 2265.7g of feed consumed. This figure was then divided by 86 (total number of feeders)—rather than 43 (total number of animals)—to determine mean food consumption per animal. The resulting incorrect number (26.35g, half the correct figure of 52.69g) was used as a denominator\* in the mg/kg formula resulting in double the mg of compound per kg of feed:

$$\frac{\text{Dosage Level} \times 7 \text{ days} \times \text{Average Body Wt.}}{\text{*Average Food Consumed}} = \text{compd./1 kg feed}$$